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Relationships between dementia risk and protective lifestyle factors with cognition and brain function in midlife

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Summary

Dementia, particularly Alzheimer's disease (AD), is a growing epidemic that presents profound challenges to healthcare systems, families, and societies throughout the world. Midlife is a critical period for the beginning of AD pathology and potentially a unique disease-altering window prior to the manifestation of substantial brain damage. Therefore, there is an urgent need for risk reduction interventions focused on midlife. However, the indicators and brain mechanisms of AD in midlife and the impact of modifiable lifestyle factors on the incipient disease process remain poorly understood. Answers to these research questions will help facilitate early prevention and intervention strategies to delay or prevent the incidence of dementia.

Chapter 2 investigated associations of established risk factors for late-onset sporadic AD with cognition and functional connectivity (FC) between the Locus Coeruleus (LC) and the hippocampus – two key brain structures in AD neuropathology – cross-sectionally and longitudinally in cognitively healthy middle-aged individuals (40-59 years). Neuropsychological assessments and resting-state functional MRI were obtained at baseline (N=210) and two-years follow-up (N=188). Associations of cognition and FC with apolipoprotein ε4 (APOE ε4) genotype, family history of dementia (FHD), and Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score were investigated. Cross-sectionally, APOE ε4 genotype was significantly associated with better episodic and relational memory, whereas higher CAIDE scores were associated with worse verbal, visuospatial functions, and short-term (conjunctive) memory. Furthermore, CAIDE score significantly moderated the relationship between cognition and LC–Hippocampus FC. Longitudinally, the LC–Hippocampus FC decreased significantly over two years.

Chapter 3 investigated the vulnerability of intrinsic brain networks to loss of functional segregation, an emerging measure of brain health, during the healthy adult lifespan and in cognitively healthy middle-aged individuals at risk for late-onset AD. Functional segregation was measured using the participation coefficient (Pc) metric under a graph-theoretic framework. Linear relationships of functional segregation with age and cortical grey matter volume (GMV) were first assessed in a healthy adult lifespan cohort (18-88 years, N=652). Associations between functional segregation and AD risk factors were then examined cross-sectionally and longitudinally, using the same midlife cohort as in Chapter 2. Across the adult lifespan, functional segregation was positively associated with GMV and

negatively associated with age, replicating previous findings. Three high-order networks [default mode (DMN), frontal-parietal control, and salience] and two sensorimotor networks (visual and motor) showed significant age effects. At midlife, cross-sectionally, the APOE ε4 allele was associated with higher functional segregation at baseline. The DMN was the only individual network to show such an effect of the APOE ε4 genotype. Higher global and DMN segregation was associated with better episodic and relational memory. Longitudinally, APOE ε4 carriers, but not non-carriers, showed a significant loss of segregation in the DMN over two years.

Chapter 4 examined the impact of modifiable lifestyle activities on AD risk-related changes in the brain and cognition in midlife. Lifestyle activities were measured using the Lifetime of Experiences Questionnaire. First, midlife activities, AD risk factors, and their interactions with cognition were examined. Then, the moderation effect of midlife activities on the relationships between measures of brain structural (total grey matter volume) and functional (global Pc) health, and cognition was investigated. Finally, the moderation effect was assessed in people at different risks of future dementia. More frequent engagement in physically, socially and intellectually stimulating activities was associated with better episodic and relational memory. Critically, more frequent engagement in these activities was associated with better verbal, visuospatial functions, and short-term (conjunctive) memory in people with FHD. In addition, these activities moderated the relationship between functional network segregation and verbal, visuospatial functions, and short-term (conjunctive) memory. Cognition was decoupled from brain functional health in individuals with more engagement in these stimulating activities, particularly those with a higher CAIDE score (CAIDE > 6).

Taken together, these findings shed light on some of the earliest effects of AD risk and modifiable lifestyle activities on cognition and brain function, and thus have implications for early detection and intervention in AD. In addition, they highlight the importance of targeting specific modifiable lifestyle activities for the prevention of AD, especially in individuals with a particular risk profile.

List of Publications and Presentations

This thesis incorporates material already published or currently under review in the following manuscripts:

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The following are presentations arising from this work:

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Deng, F., Dounavi, M. E., Ritchie, K., Muniz-Terrera, G., Malhotra, P., Ritchie, C. W., Lawlor, B., Naci, L. Disrupted role of the connectivity between the locus coeruleus and the hippocampus in cognition of healthy, middle-aged individuals at risk of dementia: the PREVENT-Dementia study. Oral presentation at *PREVENT-Dementia General Assembly, Cambridge, UK, October 2022*

Deng, F., Ritchie, K., Muniz-Terrera, G., Malhotra, P., Ritchie, C. W., Lawlor, B., Naci, L., Hyper segregation of functional brain networks and accelerated age-related segregation loss in mid-life cognitively healthy APOE-ε4 carriers. Poster presentation at *PREVENT-Dementia General Assembly, Cambridge, UK, October 2022*

Deng, F., Naci, L., Functional segregation in asymptomatic midlife individuals at genetic risk for Alzheimer's disease. Poster presentation at *Organisation for Human Brain Mapping, hybrid (virtual), June 2022*

Deng, F., Stewart, E., Naci, L., Brain network integrity across the lifespan and its relationship to cognition. Oral presentation at *Neuroscience Ireland Meeting, Virtual, September 2021*

Deng, F., Naci, L., Functional connectivity of the locus coeruleus with hippocampus and cognitive profiles in asymptomatic midlife individuals at risk for Alzheimer's disease. Poster presentation at *Organisation for Human Brain Mapping, Virtual, June 2021*

Deng, F., Naci, L., Cognition alterations of subjects at increased risk of dementia. Poster presentation at *The Brain Conference, Virtual, March 2021*

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List of Abbreviations

AD	Alzheimer's disease
MCI	Mild Cognitive Impairment
APOE	Apolipoprotein E ε4
FHD	Family history of dementia
CAIDE	Cardiovascular risk factors, Ageing and the Incidence of Dementia
fMRI	functional Magnetic Resonance Imaging
sMRI	structural Magnetic Resonance Imaging
ASL	Arterial spin labeling
LC	Locus coeruleus
FC	Functional connectivity
DMN	Default Mode Network
FPN	Frontal-Parietal Control Network
CON	Cingulo-Opercular Control Network
SN	Salience Network
DAN	Dorsal Attention Network
VAN	Ventral Attention Network
CR	Cognitive reserve
WM	White matter
GM	Grey matter
CSF	Cerebrospinal fluid
NFT	Neurofibrillary tangle
Aβ	beta-amyloid
pTau	Hyperphosphorylated tau
FD	Framewise displacement
GMV	Grey matter volume

ICV	Intracranial volume
FOV	Field of view
Pc	Participation coefficient
LEQ	The Lifetime of Experiences Questionnaire
FDR	False discovery rate
CI	Confidence interval
GLM	General linear model

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1. Chapter 1: General Introduction

This thesis investigates the impact of risk factors for late-life Alzheimer's disease (AD) on the brain and cognition in midlife, and whether protective lifestyle activities can start to offset risk effects decades before the overt manifestation of clinical symptoms. These questions have important implications for the design of early prevention and intervention strategies that may reduce the future incidence of dementia. In this Introduction chapter, I first discuss the global epidemic of dementia and how midlife serves as a potential starting point for AD pathology. I then discuss the well-established modifiable lifestyle risk factors that contribute to dementia incidence and highlight the importance of early detection and intervention for AD in midlife. Next, I present a multicentre international research programme, PREVENT-dementia, which aims to detect and intervene in AD during midlife. I then summarise the current understanding of how established risk factors affect cognition and the brain in midlife and identify research gaps that will be addressed in this thesis. I also discuss the potential contribution of protective lifestyle factors to cognitive reserve in midlife. Finally, I conclude the chapter with a brief summary of the overall thesis.

1.1 The global dementia epidemic and Alzheimer's disease

Dementia is a rapidly growing public health issue that presents profound challenges to health care systems, families, and societies throughout the world (Prince et al., 2015). It is characterized by memory loss, cognitive decline, and reduced ability to carry out daily tasks (McKhann et al., 2011). According to a global status report released by the World Health Organization in 2021, the estimated number of people living with dementia worldwide was around 55 million in 2019 and is anticipated to triple by 2050. The estimated global cost of dementia is projected to rise from US$ 1.3 trillion in 2019 to almost US$ 2.8 trillion in 2030

(World Health Organization, 2021). In the UK and Ireland, it is estimated that one million people will have dementia by 2023. In the absence of effective pharmacological treatments, there is an immediate need for early identification, intervention, and risk burden modification for dementia (Livingston et al., 2020; Ritchie et al., 2022).

Alzheimer's disease is the most common cause of dementia, accounting for 60%-80% of cases ("2023 Alzheimer's disease facts and figures," 2023). AD is neuropathologically characterized by the accumulation of beta-amyloid (Aβ) and hyperphosphorylated tau (pTau) (Braak & Braak, 1991; Braak et al., 2011). The aetiology of the sporadic form of AD remains poorly understood. The amyloid hypothesis, which dominates the AD field, proposes that the accumulation of amyloid beta initiates and drives the accumulation of tau pathology, which disables and kills neurons (Hardy & Selkoe, 2002). Consistent with this hypothesis, a popular model of the progression of AD biomarkers suggests that the accumulation of amyloid beta initiates AD when individuals are cognitively healthy. This process is followed by the accumulation of tau pathology and structural brain atrophy, with cognitive impairment manifesting relatively late relative to the initial accumulation of aberrant amyloid and tau proteins (Jack et al., 2010). Based on this modelling work and on studies of neuropathological staging, it is now well accepted that the pathological AD process starts decades before the overt manifestation of clinical symptoms (Sperling et al., 2011). However, the linear relationship with amyloid as the trigger and tau as the bullet has been challenged by recent evidence from neuropathological data (Arnsten et al., 2021) and by the limited success of neuropharmacological pursuits driven by the amyloid hypothesis (Reitz, 2012; Roberson & Mucke, 2006). Alternatively, tau deposition has been suggested to be a key aetiological factor that presages sporadic AD (Arnsten et al., 2021; Jacobs et al., 2021; Kametani & Hasegawa, 2018). Analyses of thousands of human brains across the lifespan show that the accumulation of tau pathology begins about a decade before the formation of

Aβ plaques (Braak & Del Tredici, 2015). In addition, tau pathology, but not Aβ, correlates with progressive grey matter loss (La Joie et al., 2019) and cognitive impairment (Giannakopoulos et al., 2003).

In particular, neuropathological findings show that tau pathology starts in late young adulthood and early midlife (30–40years), in the subcortical nucleus locus coeruleus (LC) (Braak & Braak, 1991), the key brain site for the production of noradrenaline. It spreads initially to the transentorhinal and entorhinal cortex (Braak et al., 2011), then to the hippocampal and neocortical association cortex, and eventually throughout the neocortex. By contrast, Aβ plaques are purportedly first deposited in the association neocortex of the temporal lobe, and then extend throughout the cortex, including subcortical structures, with disease progression (Braak & Del Tredici, 2015). Therefore, brain changes related to sporadic AD in early midlife (i.e., 40-50 years) are likely associated with neurodegeneration from pTau deposition, and, in older age groups, Aβ plaques additionally contribute strongly to the underlying neurodegeneration.

1.2 Modifiable lifestyle risk factors contribute to dementia incidence.

Recent epidemiological data provide strong evidence that modifiable lifestyle-related risk factors are closely linked to the development of dementia. Studies have shown that up to 40% of dementia cases are attributable to known lifestyle risk factors, such as alcohol consumption, obesity, and hypertension among others (Livingston et al., 2020; Norton et al., 2014). Moreover, exposure to these risk factors often begins in midlife or even earlier, decades before the onset of dementia symptoms. For example, midlife vascular risk factors have been found to significantly impact the incidence of dementia over a 25-year period (Gottesman, Albert, et al., 2017; Walker et al., 2019), and may contribute to elevated Aβ

deposition for more than 20 years (Gottesman, Schneider, et al., 2017). Midlife depression has been significantly associated with compromised memory function in cognitively healthy middle-aged individuals (Ritchie et al., 2021). Taken together, these findings suggest that interventions targeting modifiable risk factors need to be implemented in midlife to be most effective in reducing the risk of developing dementia in later life and improving overall cognitive and brain health (Gottesman, Albert, et al., 2017; Gottesman, Schneider, et al., 2017; Irwin et al., 2018; Lachman et al., 2015). Midlife, thus, presents a unique and critical window for disease-altering interventions, before the manifestation of substantial brain damage (Ritchie et al., 2015).

Overall, growing neuropathological and epidemiological evidence highlights the importance of detecting and intervening in AD in the potential incipient period – midlife, prior to the manifestations of substantial brain damage and clinical symptoms (Barnes & Yaffe, 2011; Livingston et al., 2017; Ritchie et al., 2010). However, the indicators and brain mechanisms of AD in midlife (Irwin et al., 2018; Ritchie et al., 2017), and the impact of stimulating lifestyle activities on the incipient disease process, remain poorly understood. Therefore, a necessary preliminary step to future large-scale interventions is the development and validation of sensitive biomarkers of early Alzheimer's disease process, which will enable the evaluation of interventions in the short term.

1.3 The multicentre international PREVENT-dementia research programme

The multicentre international PREVENT-dementia research programme is designed to address these critical knowledge gaps (Ritchie & Ritchie, 2012). PREVENT is a prospective cohort study of the middle-aged adult children of persons with dementia, designed to seek out clinical and biological changes, which may subsequently be used as short-term outcome

measures for midlife secondary preventions. PREVENT also recruits a control group of middle-aged adult children of persons without dementia. By profiling midlife risk factors for late-life neurodegenerative disease and identifying the earliest indices of disease development, PREVENT represents one of the epidemiological initiatives targeting midlife as a critical window for intervention in neurodegenerative conditions. This research programme was initiated in 2014 in a single site, at Imperial College London, and was subsequently expanded to become a multi-centre study, including sites at the universities of Cambridge, Oxford, and Edinburgh in the UK, and Trinity College Dublin in Ireland.

Across these five research centres, deep phenotyping datasets have been collected cross-sectionally and longitudinally over two years in a large cohort (N=700, half with a family history of dementia (FHD) and half without), including clinical samples (blood, saliva, and urine sampling), neuroimaging data (brain structural and functional imaging), a set of well-established computerized cognitive tests designed to cover a much wider range of cognitive functions than is normally used in studies of preclinical dementia (Hartley et al., 2007; Parra et al., 2010; Ritchie, 2014; Tu et al., 2015), as well as questionnaires recording midlife lifestyle activities (e.g., occupational/ managerial responsibility, leisure time activities, and sleep, etc.) and mental health (e.g., depression, anxiety, stress, and resilience, etc.).

Previous studies on preclinical AD have used risk stratification approaches to investigate early, preclinical changes. Accordingly, key risk factors considered in the PREVENT-dementia program are Apolipoprotein E (APOE) ε4 genotype (Donix et al., 2012; Liu et al., 2013), the main genetic risk factor for sporadic late-onset AD in the Indo-European population (Lambert et al., 2013), and FHD (Donix et al., 2012; Scarabino et al., 2016). Several dementia risk scores incorporating lifestyle risk factors have been devised (Barnes et al., 2014; Deckers et al., 2015; Kivipelto et al., 2006). Amongst them, the Cardiovascular risk factors, Ageing and the Incidence of Dementia (CAIDE) score, incorporating age, sex,

education, systolic blood pressure, body mass index (BMI), total cholesterol, physical activity, and APOE ε4 genotype, has been optimized for middle-aged populations (Kivipelto et al., 2006) and validated in a large US population followed longitudinally over 40 years (Exalto et al., 2014).

The principal hypothesis of the PREVENT-dementia programme is that middle-aged persons at high risk of late-life dementia (FHD positive, APOE ε4 carriers, or with a high CAIDE score) will show significant differences in amyloid, tau, p-tau, inflammatory markers, medial temporal lobe (MTL) atrophy, white matter lesions, and other neuroradiological outcomes, cognitive performance targeting LC, transentorhinal and hippocampus, and HPA axis dysregulation in comparison to persons with low risk. Biomarkers are examined cross-sectionally and prospectively over two years in persons 40 to 59 years old. The ability to explore the effect of AD risk factors on presently cognitively healthy middle-aged individuals longitudinally offers the opportunity for invaluable insights into the impact of time on risk-related cognitive and brain changes.

1.4 Evidence on the impact of risk factors on *cognition* in midlife

Studies of the PREVENT and other similar cohorts of cognitively healthy midlife individuals have related the three risk factors – APOE ε4 genotype, FHD, and CAIDE score – to cognitive changes in midlife. APOE ε4 carriers have been significantly associated with better performance in immediate recall (Jochemsen et al., 2012), form perception (Ritchie et al., 2017), and narrative recall (McKiernan et al., 2020) relative to non-carriers. How may these beneficial effects of the APOE ε4 genotype be explained? The better performance in middle-aged APOE ε4 carriers may underlie a compensatory response, which, in the presence of incipient AD-related pathology, supports more efficient cognitive performance (Cacciaglia

et al., 2022). These results may also be interpreted based on the antagonistic pleiotropy hypothesis of aging (Williams, 1957), which proposes that deleterious genes, such as the APOE ε4 gene allele, have survived through evolution because they might confer an advantage early in life, when humans are reproductively fit.

FHD has been associated with poorer verbal processing and memory performance in participants under 65 years (Talboom et al., 2019) as well as poorer executive function (Debette et al., 2009; Ritchie et al., 2017). Higher CAIDE scores have been associated with poorer memory functions (Low et al., 2022; Ritchie et al., 2017), visuospatial and navigational abilities (Ritchie et al., 2018; Ritchie et al., 2017), processing speed, and executive function (Low et al., 2022; Stephen et al., 2017), as well as language ability (Ritchie et al., 2017). However, previous studies have either focused on only one or a few individual cognitive functions, limiting the ability to compare the results across studies, or have failed to control for multiple comparisons when examining a number of functions simultaneously, which can increase Type I error and result in false positive findings (Ranganathan et al., 2016). In addition, most of the evidence to date has been cross-sectional, and there is a lack of knowledge about whether these risk factors also affect cognition longitudinally. Further research is therefore needed to understand better the relationship between established AD risk factors and cognitive decline over time in middle-aged people. Overall, while previous studies provide important insights into the vulnerability of cognitive function to Alzheimer's disease risk in midlife, it is important to consider the current limitations and the need for further research in this area. Addressing these gaps is the focus of the work described in Chapter 2.

1.5 Evidence on the impact of risk factors on the *brain* in midlife

Studies of cognitively healthy midlife individuals have also related the three aforementioned risk factors to a range of structural and functional brain changes. APOE ε4 genotype has been associated with compromised structural brain integrity, including loss of volume in the hippocampal molecular layer (Dounavi et al., 2020), reduced grey matter volume in the right hippocampus, caudate, precentral gyrus, and cerebellar cortex (Cacciaglia et al., 2018), decreased cortical thickness in the frontal cortex (Fennema-Notestine et al., 2011), declined white matter integrity (Operto et al., 2019), and longitudinal progression of white matter hyperintensities (Low et al., 2021). By contrast to brain structural changes, studies investigating the impact of APOE ε4 genotype on brain function have so far revealed marked variability in the directionality of changes in midlife, using both task-related and resting-state functional Magnetic Resonance Imaging (fMRI) techniques (see also reviews Habib et al. (2017); Kucikova et al. (2021)). For example, compared with non-carriers, APOE ε4 carriers showed reduced activation in the hippocampus and MTL to an episodic encoding task (Trivedi et al., 2006), and reduced functional connectivity in these brain areas (Sheline, Morris, et al., 2010) and in the default mode network (DMN) during resting state (Goveas et al., 2013; Patel et al., 2013). However, hyperactivation in the fronto-parietal network to a working memory task (Chen et al., 2013) and hyperconnectivity in the DMN (Fleisher, Sherzai, et al., 2009) and salience network (SN) during resting state (Goveas et al., 2013) have also been reported in middle-aged APOE ε4 carriers relative to non-carriers. In line with these fMRI studies, previous Arterial Spin Labelling (ASL) studies have also shown regional cerebral hyper-perfusion in middle-aged APOE ε4 carriers compared to non-carriers (Dounavi et al., 2021; Fleisher, Podraza, et al., 2009; Mak et al., 2021; McKiernan et al., 2020).

What might be the reason for the lack of consistency in the directionality of functional brain

changes related to the APOE ε4 genotype in midlife? A methodological limitation that may underlie these inconsistent findings is statistical power. To date, most studies investigating the effect of APOE ε4 genotype on fMRI changes in midlife have included fewer than 20 participants (Habib et al., 2017; Kucikova et al., 2021). In addition, there is a lack of longitudinal studies to describe changes over time. Therefore, large-scale longitudinal studies, with a specific focus on midlife, are key to further testing this hypothesis.

In addition, FHD has been found to be associated with volumetric alterations in hippocampal subfields (McKeever et al., 2020; Okonkwo et al., 2012), reduced grey matter volume in the right precuneus (Ten Kate et al., 2016), disrupted white matter integrity (Bendlin et al., 2010; Mak et al., 2021; Sánchez et al., 2020), progression of white matter hyperintensities (Low et al., 2021), regional cerebral hyperperfusion (McKiernan et al., 2020), greater activation in the hippocampus during a spatial memory encoding task (Rajah et al., 2017), and reduced activity in the dorsal cuneus and medial frontal cortices during an episodic recognition task (Xu et al., 2009). The CAIDE score has been associated with whole brain atrophy (Liu et al., 2021; O'Brien et al., 2020; Ritchie et al., 2017), hippocampal volume loss (McKeever et al., 2020; Ritchie et al., 2017), reduced grey matter volume in the temporal, occipital, and fusiform cortex (Liu et al., 2021), decreased cortical thickness in the precuneus, superior frontal, inferior parietal, and middle temporal cortex (Dounavi et al., 2022; Gourley et al., 2020), and the severity and progression of the white matter hyperintensities (Low et al., 2022; Salvadó et al., 2019).

A common finding from these previous studies is that all three AD risk factors are associated with volume loss of the entire hippocampus or its specific subfields in cognitively healthy middle-aged individuals (Cacciaglia et al., 2018; Dounavi et al., 2020; McKeever et al., 2020; Okonkwo et al., 2012; Ritchie et al., 2017). The hippocampus is involved in the early stages of AD pathology (Braak & Braak, 1991) and is, therefore, particularly vulnerable to

neurodegeneration in the early disease process (Dounavi et al., 2020). Therefore, hippocampus changes may provide an early indication of increased risk for future AD. Given its important role in memory consolidation and spatial navigation (Lisman et al., 2017), disruption of the hippocampus may also significantly affect cognition in the early stages of AD. However, it remains unclear whether the functional properties of the hippocampus, such as its connectivity with other brain regions, are also affected in midlife in relation to these established risk factors. Functional connectivity refers to the degree to which different brain regions are synchronized in their activity and communication (van den Heuvel & Hulshoff Pol, 2010). Investigating functional connectivity can therefore provide insights into how the hippocampus interacts with other brain regions, which is important for understanding the mechanisms underlying the early stages of AD, and, thus, for developing early diagnostic and intervention strategies.

One candidate region whose connectivity to the hippocampus is of particular interest is the locus coeruleus, a small nucleus located in the brainstem that plays a critical role in regulating wakefulness, attention, and stress response (Van Egroo et al., 2022). As discussed above, a recent neuropathological staging framework suggests that the accumulation of tau pathology, one of the hallmarks of AD, begins in the LC (Arnsten et al., 2021), and, therefore, structural and functional alterations in this brain area are important for pinpointing early disease processes. Animal and human studies have also demonstrated the importance of LC integrity for successful spatial learning and memory (Jacobs et al., 2015; James et al., 2021; Kaufman et al., 2020; Kempadoo et al., 2016; Sara, 2009). Furthermore, a recent study of asymptomatic middle-aged adults found that functional connectivity between the LC and cerebellum was significantly reduced in individuals with FHD compared to those without (Del Cerro et al., 2020). Given the key importance of the LC and the hippocampus for memory function, and their etiological role in AD progression, investigating functional

connectivity between these two regions may provide key insights into the mechanisms underlying the spread of tau pathology and its potential impact on cognition in the earliest stages of the disease. While accumulating evidence indicates that, individually, the LC and the hippocampus are affected in midlife by the risk of late-life AD (Del Cerro et al., 2020; Fleisher, Sherzai, et al., 2009; Trivedi et al., 2006); (for a review see Habib et al. (2017)), it remains unknown whether their interactions and joint role in cognition are affected by AD risk at this stage.

Furthermore, there is evidence that alterations in functional connectivity may occur prior to macroscale brain structural changes (Fox & Raichle, 2007; Greicius et al., 2004). Indeed, previous research has indicated that functional brain changes are an early occurrence among individuals at risk for Alzheimer's disease (Habib et al., 2017). Few studies have concomitantly assessed cognitive performance in relation to functional brain changes. Unravelling this relationship may not only help to elucidate the mechanisms through which AD risk factors impact cognitive outcomes in the short term in midlife, and but also facilitate the interpretation of early functional brain changes, for which there is currently no consensus as discussed above (Habib et al., 2017; Kucikova et al., 2021). Therefore, the investigation of functional brain changes, such as functional connectivity between the LC and hippocampus, and their relationships to cognitive outcomes in at-risk individuals has the potential to provide valuable insights into the early development of AD and inform early interventions. Addressing these gaps is the focus of the work described in Chapter 2.

Although accumulating evidence points to functional brain changes as an early event in individuals at risk for AD (Habib et al., 2017), as discussed above, there is a lack of consensus on the directionality of the changes. A potentially sensitive functional marker for identifying at-risk individuals in the early stages of Alzheimer's disease is intrinsic brain network organisation (Kucikova et al., 2021). Resting-state fMRI techniques provide a tool

to examine the correlation between intrinsic oscillations or temporal patterns of the blood oxygenation level-dependent (BOLD) signal between brain regions at rest, and have identified several brain networks that show synchronous spontaneous activity across widely distributed brain areas (Biswal et al., 1995; Fox et al., 2005; Greicius et al., 2003; Lowe et al., 2000; Raichle et al., 2001). Those identified intrinsic brain networks are associated with specialised functional processing (Sporns & Betzel, 2016; Wig, 2017). Recent studies have shown that functional changes in brain networks critical for memory function, such as the DMN, SN, and executive control network (ECN), are present in asymptomatic individuals with subjective cognitive decline, a putative precursor of dementia (see a recent review Viviano and Damoiseaux (2020)). Thus, analysis of the functional brain network organization may have the potential to elucidate early brain changes associated with AD risk with high sensitivity (Kucikova et al., 2021). However, very little is currently known about the impact of AD risk factors on brain network organization in midlife.

Graph theoretical approaches are commonly used to study the organisation of brain networks (Bullmore & Sporns, 2009). In a graphic representation, a brain network is defined in graph theory as a set of nodes, i.e., brain regions, and the edges, i.e., functional connectivity between them (Bullmore & Sporns, 2009). The human brain has been found to exhibit complex network properties such as small-world topology, highly connected hubs and modularity (Bullmore & Sporns, 2009; Sporns & Betzel, 2016). The small-world property enables highly efficient information processing throughout the brain by combining high levels of local clustering between brain nodes, i.e., segregation, with short paths that globally connect all brain nodes, i.e., integration (Bassett & Bullmore, 2017; Liao et al., 2017; van den Heuvel et al., 2008). As it measures the balance between network segregation and integration, it has been widely studied in Alzheimer's disease (Dai et al., 2019; Stam et al., 2007; Supekar et al., 2008; Tijms et al., 2013).

Moreover, the functional segregation of brain networks has recently emerged as an important indicator of brain health (Wig, 2017). Network segregation describes the extent to which different brain networks, such as primary sensory networks, i.e., visual and auditory networks, or higher order networks, i.e., DMN, SN and ECN, are distinct from each other (Wig, 2017). Recent studies have shown that increasing adult age is associated with reduced network segregation, or more diffuse functional organisation of the brain. Such 'de-differentiation' of functional brain networks is in turn associated with age-related decline in cognitive and motor functions across the healthy adult lifespan (Chan et al., 2014; King et al., 2018; Kong et al., 2020; Manza et al., 2020; Pedersen et al., 2021; Varangis et al., 2019). Furthermore, loss of network segregation has also been observed at different stages of the AD process, such as in asymptomatic older adults with increasing accumulation of AD pathology (Brier et al., 2014; Ewers et al., 2021), in mild cognitive impairment (MCI) (Farràs-Permanyer et al., 2019; Jiao et al., 2021) and in AD patients (Dai et al., 2019; Ewers et al., 2021). It has also been found that asymptomatic older adults with genetic risk, i.e. the presence of the APOE ε4 gene allele, have reduced functional segregation in higher order networks – DMN, SN and ECN – compared to those without (Ng et al., 2018). However, it remains unknown whether AD risk factors affect brain network segregation in cognitively healthy middle-aged individuals.

Furthermore, individual networks may exhibit selective vulnerability to early AD processes. The DMN is of particular interest, as studies have consistently shown disrupted functional integrity of the DMN in AD (Cha et al., 2013; Jones et al., 2011; Koch et al., 2012). This disruption is associated with cognitive impairment and severity of disease progression (Greicius et al., 2004; Lustig et al., 2003; Zhang et al., 2010). Understanding whether AD risk factors disrupt the functional integrity of the DMN in midlife may provide new insights

into the early development of the disease. Addressing these gaps is the focus of the work described in Chapter 3.

1.6 The role of protective lifestyle factors on cognitive reserve in midlife

The studies summarised above have shown that lifestyle-related risk factors for late-onset AD have a significant impact on brain health and cognition in middle-aged individuals who are presently cognitively healthy. As a multidimensional construct, lifestyle has a multipronged impact on brain health and cognition. By contrast to lifestyle risk factors such as those captured by the CAIDE score, some lifestyle factors confer protection on brain health and cognition across the lifespan. In this section, I discuss the current evidence on the contribution of midlife lifestyle activities to late-life cognitive reserve and highlight the research gap as to whether the contribution of midlife lifestyle to cognitive reserve begins in midlife.

Cognitive reserve has been widely recognized in the context of ageing and Alzheimer's disease. Prospective studies of ageing have shown that up to 25% of older people who are cognitively unimpaired before death meet the full pathological criteria for Alzheimer's disease (Esiri et al., 2001). The discrepancy between the accumulation of brain pathology and its clinical manifestations can be explained by the concept of cognitive reserve (Stern, 2009, 2012; Stern et al., 2020). Cognitive reserve refers to the adaptability of cognitive and functional brain processes, which helps to account for individual differences in cognition or clinical manifestations in response to brain ageing and pathology (Stern et al., 2020). It is thought that people with greater adaptability of these processes, i.e., greater cognitive reserve, are better able to cope with brain ageing and pathology and thus maintain normal cognition (Stern et al., 2020).

Individual differences in these pre-existing cognitive and functional brain processes are, by definition, what determines cognitive reserve. These processes can be influenced by the interaction of genetics and lifetime exposures (Stern et al., 2020). Several lifestyle activities have been found to counteract age- or disease-related brain decline to preserve cognitive function in older adults (D. Chan et al., 2018; Stern, 2009) and reduce risk of developing dementia (Scarmeas et al., 2001; Stern et al., 1994; Valenzuela & Sachdev, 2006) and symptom severity in Alzheimer's disease (Dekhtyar et al., 2019; Livingston et al., 2020), supporting the cognitive reserve hypothesis. In particular, education (Kremen et al., 2019; Richards & Deary, 2005), occupational attainment (Smart et al., 2014; Suo et al., 2012), and physically, socially and intellectually stimulating activities (Chaddock-Heyman et al., 2021; Duzel et al., 2016) have been identified as key drivers of cognitive reserve. In other words, these factors are thought to explain why, in late-life AD, the level of cognitive impairment shows substantial variability even when accounting for key pathologies, including Aβ and pathological tau (Franzmeier et al., 2020; Jack & Holtzman, 2013).

Accurate measurement of cognitive reserve has important implications for the development of interventions aimed at enhancing cognitive reserve in order to reduce or prevent cognitive decline and dementia. It would help to identify the determinants of cognitive reserve, which could then be targeted by behavioural and lifestyle interventions. A valid investigation of cognitive reserve requires three components: a putative measure of cognitive reserve, such as a proxy or a candidate neuroimaging measure, a measure of brain structure/pathology, and a measure of cognitive function (Christensen et al., 2008; Stern et al., 2020). It also requires a complete model that includes all three components, where the putative measure of cognitive reserve is not only associated with cognitive performance, but also moderates the relationship between the measure of brain health and cognition (D. Chan et al., 2018;

Song et al., 2022). Demonstrating a moderation effect is considered the strongest level of evidence for a measure of cognitive reserve (Stern et al., 2020).

Moreover, cognitive reserve is not fixed. At any point in a person's life, it results from a combination of exposures. There is increasing interest in the contribution of activities that, unlike the majority of education, are undertaken in midlife, given their modifiability during this period. For example, Gow et al. (2017) and D. Chan et al. (2018) used the Lifetime of Experiences Questionnaire (LEQ) and found that physically, socially and intellectually stimulating lifestyle activities undertaken in midlife, independent of education, help to maintain late-life cognitive performance in older adults, after adjusting for childhood cognitive ability (Gow et al., 2017). A different study by Palta et al. (2021) found that more engagement in physical activities in midlife was significantly associated with more intact white matter integrity and lower cerebrovascular lesions in late life. However, it is not known whether the protection conferred by lifestyle activities, other than education, offsets the impact of AD risk in midlife, or whether it builds up gradually over time with its benefits detectable only in late life or relative to established AD pathology. The answer to this question is critical for identifying interventions that target modifiable factors for the prevention of Alzheimer's disease from the earliest life stages. Addressing this gap is the focus of the work described in Chapter 4.

1.7 Overview of the thesis

Based on the research reviewed in this chapter, there is a clear need to investigate (a) brain functional changes and brain-cognition relationships with respect to the well-established risk factors for AD, and (b) the effect of stimulating lifestyle activities undertaken in midlife on those brain and cognitive changes in healthy middle-aged individuals at risk of developing

late-onset AD. Chapter 2 and Chapter 3 aim to address the first broad research question, and Chapter 4 aims to address the second. The baseline and two years follow-up data from the pilot phase (N =210) of the PREVENT-Dementia research programme carried out at the Imperial College London site were used to investigate cross-sectional and longitudinal relationships in the three data chapters. I chose to focus on this well-curated dataset because, unlike the whole PREVENT cohort for which follow-up data is still being acquired, it contains both baseline and follow-up assessments.

Chapter 2 investigated whether the risk of late-life AD would be significantly associated with cognition, LC–Hippocampus functional connectivity, and their brain–behaviour relationship in cognitively healthy midlife individuals. Furthermore, I investigated whether risk factors would be associated with longitudinal change in cognition and functional connectivity in this cohort. I used a dimensionality reduction technique to extract the common cognitive domains underlying a set of sensitive tests for detecting early changes in AD. This technique could improve the statistical power to detect underlying effects, given a myriad of cognitive variables available in the dataset. The impact of the three risk factors – APOE ε4 genotype, FHD, and CAIDE score – on cognition and the LC–Hippocampus functional connectivity were first investigated. If either cognition or functional connectivity showed an effect of the risk factors, their relationship was further investigated in relation to the risk factors. My hypothesis was that individuals with higher risk of late-onset AD would show impaired cognition and LC–Hippocampus functional connectivity compared to those at low risk. Furthermore, I expected that risk factors would be associated with longitudinal changes in cognition and functional connectivity.

Chapter 3 investigated risk-related changes of an emerging measure of brain health – the segregation of functional brain networks (Ewers et al., 2021; Wig, 2017) – in the same cognitively healthy middle-aged cohort at risk of developing AD. The segregation property

of brain network organization is recognized as an important indicator of brain health in both normal and pathological ageing. It decreases with age across the adult lifespan, and is positively associated with cognitive performance in healthy ageing, and inversely associated with symptom severity in AD. However, it remains unknown (i) which brain networks are vulnerable to age- and disease-related changes in functional segregation, and (ii) whether functional network segregation is affected by established AD risk factors in midlife. This chapter sets out to answer these two research questions. The segregation of global and individual networks was first assessed in relation to age, by using an open-access lifespan dataset collected by the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) research programme. I then assessed the functional segregation in relation to the three well-established risk factors for late-onset AD in the PREVENT cohort. My hypothesis was that high-order networks are expected to show the strongest age effect across the healthy adult lifespan. Furthermore, in cognitively healthy middle-aged adults, the global segregation of functional networks, and the segregation of networks most susceptible to the healthy ageing processes would be influenced by the risk of late-onset AD.

Chapter 4 investigates whether stimulating lifestyle activities contribute to cognitive reserve in midlife. I asked three research questions: (i) whether stimulating lifestyle activities interact with risk factors to influence cognition; (ii) whether stimulating lifestyle activities moderate the relationship between structural and functional brain measures and cognition; and (iii) whether such moderation differs by risk group. Midlife lifestyle activities were measured by using the Lifetime of Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007). The LEQ is designed to take a lifespan approach to the measurement of a broad range of lifestyle activities across three stages of life: young adulthood (13-29 years), midlife (30-64 years) and late life (65 years onwards). The LEQ was used to evaluate lifestyle activities specific to midlife in the PREVENT study, yielding two composite factors,

(a) occupation and managerial responsibility, and (b) physical, social and intellectual activities. My hypotheses were (i) that there would be positive associations of midlife stimulating lifestyle factors with cognition in domains already shown in this cohort to be affected by risk of late-life AD; and (ii) that midlife stimulating lifestyle factors would significantly moderate the relationship between brain health and cognition, in such a way that cognition of individuals with more engagement in stimulating lifestyle activities would be less dependent on typical measures of brain health, in line with a rigorous definition of cognitive reserve.

2. Chapter 2: Genetic and cardiovascular risk of dementia is associated with brain–behaviour changes in cognitively healthy, middle-aged individuals

2.1 Introduction

It has been suggested that early tau pathology in the subcortical nucleus locus coeruleus (LC) induces LC hyperactivity, thereby promoting its own spread to interconnected brain regions and facilitating the progression of the disease (Weinshenker, 2018). A recent review of the neuropathological literature across the lifespan (Arnsten et al., 2021) suggests that the spread of tau pathology from the LC to the medial temporal lobe (MTL) captures the earliest stages of incipient Alzheimer's Disease (AD) progression (but see Kaufman et al. (2018) for a differing account). However, alterations of connectivity between the LC and the hippocampus due to AD risk factors have not previously been studied in midlife preclinical populations. In the first empirical study of my thesis, I aimed to address this research question by using the pilot data from the PREVENT-Dementia research programme.

LC is the earliest site of tau pathology accumulation, and, furthermore, the main brain site of noradrenaline production (Amaral & Sinnamon, 1977), and thus the originating node of the brain's arousal system (Aston-Jones & Cohen, 2005; Sara, 2009). Therefore, early LC pathology can critically impact arousal and cognitive processes throughout the brain (Betts, Kirilina, et al., 2019; Mather & Harley, 2016). Previous in vivo studies of the LC have investigated healthy lifespan adult cohorts (Betts et al., 2017; Clewett et al., 2016; Lee et al., 2020; Liu et al., 2019; Porat et al., 2022), cognitively unimpaired older adults (Jacobs et al., 2021; Prokopiou et al., 2022; Van Egroo et al., 2021), preclinical autosomal dominant

Alzheimer's disease (Jacobs et al., 2022), mild cognitive impairment (Jacobs et al., 2015; Takahashi et al., 2015), and Alzheimer's disease (Betts, Cardenas-Blanco, et al., 2019; Dahl et al., 2022; Olivieri et al., 2019; Takahashi et al., 2015) and found significant negative associations of LC integrity with age, age-related cognitive decline (Calarco et al., 2022; Dahl et al., 2019; Liu et al., 2020), AD pathology, such as amyloid (Betts, Cardenas-Blanco, et al., 2019) and tau deposition (Dahl et al., 2022; Jacobs et al., 2022), as well as with symptom severity in AD (Sun et al., 2020). However, by contrast to its key importance to cognitive function and etiological role in AD progression, there is very limited in vivo understanding of LC function disruptions during the early preclinical period. One exception is a recent study of asymptomatic midlife adults, offspring of late-onset AD (O-LOAD) patients. Del Cerro et al. (2020) found that functional connectivity of the LC and cerebellum was significantly associated with delayed recall performance, and that this functional connectivity was reduced in O-LOAD individuals relative to those without a family history.

The hippocampus is one of the first regions to demonstrate atrophy during prodromal AD. Neurofibrillary tangle (NFT) accumulation within the MTL, including the hippocampus, is one of the first hallmarks of pathological manifestations. Recent studies in cognitively healthy individuals at risk for late-life AD have found that AD risk impacts the hippocampus in midlife (Dounavi et al., 2022; Dounavi et al., 2020; Kerchner et al., 2014); (for a review, see Vilor-Tejedor et al. (2021)). Dounavi et al. (2020) reported that the volume of the molecular layer of the hippocampus was reduced in cognitively healthy midlife individuals with APOE ε4 genotype. A more recent study (Dounavi et al., 2022) reported that the hippocampal fissure was enlarged in middle-aged individuals with high CAIDE dementia risk scores.

Critically, the connectivity between the LC and the hippocampus is important for cognition. Animal studies have demonstrated that the co-release of noradrenaline and dopamine from

LC terminals in the hippocampus is critical for successful spatial learning and memory (James et al., 2021; Kaufman et al., 2020; Kempadoo et al., 2016). Human studies in healthy older adults are consistent with these data and show that higher LC–Hippocampus functional connectivity is significantly associated with better memory (Jacobs et al., 2015). While accumulating evidence indicates that, individually, the LC and hippocampus are affected in midlife by the risk of late-life AD, it remains unknown whether their interactions and joint role in cognition are affected by AD risk at this stage. Understanding changes in the interaction of LC and the hippocampus during this preclinical period in at-risk populations has the potential to not only shed light on the brain mechanisms of incipient AD, but also to provide urgently needed early disease biomarkers.

To address this gap, I investigated the impact of three risk factors for late-life AD (APOE ε4 genotype, FHD and CAIDE score) on cognition and the LC–Hippocampus functional connectivity as well as their associations. I tested a cohort of cognitively healthy middle-aged individuals at baseline (N = 210) and two-years follow-up (N = 188) with a detailed neuropsychological battery not restricted to functions usually implicated in dementia detection in older adults. Structural and functional Magnetic Resonance Imaging (MRI) data were obtained at both research visits. My hypotheses were that risk of late-life AD would be significantly associated with cognition, LC–Hippocampus functional connectivity, and their brain–behaviour relationship in middle-aged and cognitively healthy individuals. Furthermore, I expected that risk factors would be associated with a longitudinal change in cognition and functional connectivity in this cohort.

2.2 Methods

2.2.1 Participants

PREVENT-Dementia is an ongoing longitudinal multi-site research programme across the UK and Ireland, seeking to identify early biomarkers of AD and elaborate on risk-mechanism interactions for neurodegenerative diseases decades before the cardinal symptoms of dementia emerge. Its protocol has been described in detail elsewhere (Ritchie & Ritchie, 2012). In the first PREVENT programme phase, participants were recruited at a single site, via the dementia register database held at the West London National Health Service (NHS) Trust, of the UK National Health Service, the Join Dementia Research website (https://www.joindementiaresearch.nihr.ac.uk/), through public presentations, social media and word of mouth. Procedures involving experiments on human participants were carried out in accord with the ethical standards of the Institutional Review Board of Imperial College London and in accord with the Helsinki Declaration of 1975. Approval for the study was granted by the NHS Research Ethics Committee London Camberwell St Giles. Consented participants were seen at the West London NHS Trust, where they underwent a range of clinical and cognitive assessments (Ritchie & Ritchie, 2012). The cohort comprised cognitively healthy volunteers aged 40-59 years. Here I examined baseline and follow-up data from the Imperial College London dataset. 210 individuals (62 male; 148 female) were tested at baseline, with 188 (89.5%) (55 male; 133 female) retained at two-year follow-up (Table 2.1). Mild cognitive impairment and dementia were ruled out based on a detailed clinical assessment on each visit.

Exclusion of participants. At baseline, 2 participants were missing APOE ε4 genotype information, and, therefore, the CAIDE scores. At follow-up, 6 participants were missing information for calculating their CAIDE scores, including the 2 missing APOE status. For cognitive tests, 2 participants were missing data at baseline, and 12 at follow-up. Therefore, the cognitive analyses cohort was N = 208/N = 176 at baseline/follow-up. 193 out of 210 participants finished MRI scanning at baseline, and 169 out of 188 at follow-up. Furthermore,

at baseline, 6 were excluded due to incidental findings, and 58 due to not meeting the criterion of > 150 frames with minimal head motion (for details, see the following section *2.2.4 MRI data acquisition and processing*). At follow-up, 3 were excluded due to incidental findings and 73 due to < 150 frames with small head motion. The final fMRI analyses cohort was N = 129/N = 93 at baseline/follow-up. Please see Appendix A and Table 6.1–6.2 and Figure 6.1 for a description of any missing data.

2.2.2 Risk factors

APOE ε4 Genotyping

The process of APOE ε4 allele identification is outlined in detail in Ritchie et al. (2017). In brief, genomic DNA was isolated from blood samples and APOE genotyping was performed. All members of the research and clinical teams were blind to the result of APOE genotyping. In this study, APOE ε4 risk is determined by ≥1 APOE ε4 allele. 75/210 carried ≥1 APOE ε4 allele (Table 2.1).

Family History of Dementia

FHD was determined by a 'yes'/'no' question during clinical visits, where participants were asked whether a parent had a diagnosis of dementia. Participants were asked to include the dementia subtype if known, but answering 'yes' alone categorized a participant as FHD+. The answer 'no' likely captured both participants with no FHD, and participants for whom FHD was unknown. In summary, participants were defined as FHD+ if at least one parent was diagnosed with dementia. Cases where the FHD was unknown or partially known were not recorded outside of the binary yes/no scoring. 103/210 were FHD+ (Table 2.1).

Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score

CAIDE is a composite scale of estimated future dementia risk based on mid-life cardiovascular measures (Fayosse et al., 2020; Sindi et al., 2015). It takes into consideration the individual's age, sex, educational attainment, APOE ε4 genotype, activity level, BMI, cholesterol and systolic blood pressure (Kivipelto et al., 2006) and is scored on a range of 0 – 18. A higher score indicates greater risk. The CAIDE dementia risk score was calculated at baseline and follow-up (Table 2.1).

2.2.3 Cognitive testing

Cognitive function was assessed at baseline and follow-up with the COGNITO neuropsychological battery (Ritchie, 2014), designed to examine information processing across a wide range of cognitive functions in adults of all ages and not restricted to those functions usually implicated in dementia detection in the older adults. Tests are administered using a tactile screen to capture information processing time as well as response accuracy and require about 40 minutes to complete. The tests, by order of presentation, are: reaction time; reading; comprehension of phonemes, phrases, and syntax; focused and divided attention in both visual and auditory modalities; visual working memory (visual tracking with auditory interference); the Stroop test; immediate, delayed, and recognition trials for verbal recall (name list); delayed recognition of spatial stimuli (faces); visuospatial associative learning; visuospatial span; form perception; denomination of common objects; spatial reasoning; copying of meaningful and meaningless figures; verbal fluency with semantic and phonetic prompts; immediate recall of a narrative; immediate recall of a description of the relative position of objects; vocabulary; implicit memory (recognition of new and previously learned material).

The COGNITO tests are designed to test several aspects of cognition, including attention (task: visual and auditory attention), memory (tasks: narrative recall, description recall, implicit memory, name-face association, working memory), language (tasks: phoneme comprehension, verbal fluency) and visuospatial abilities (task: geometric figure recognition) (Ritchie, 2014). Based on previous studies (Ritchie et al., 2021; Ritchie et al., 2018; Ritchie et al., 2017), 11 summary variables from the COGNITO battery capturing the above functions were used here (for details, see Table 6.2).

Additionally, I used the Visual Short-Term Memory Binding task (VSTMBT) (Parra et al., 2010), a computer-based task that assesses visual short-term memory binding of single features, e.g., complex shape or colour combinations, or feature conjunctions, e.g., shape and colour combinations. In the single feature condition, participants must identify whether the test stimuli (three random 6-sided polygons) are the "same" as or "different" to the studied stimuli in terms of shape (shape only) or colour (colour only). In the binding condition, participants are required to correctly identify if both the shape and colour of the test stimuli match studied stimuli. The two summary variables from the VSTMBT were the percentage of correctly recognized items from the two conditions (for details, see Table 6.2).

The Addenbrooke's Cognitive Assessment (ACE) III (Hsieh et al., 2013) was recorded at the follow-up session, but not at the baseline. Analyses that focused on the subset of assessments performed at both testing sessions did not include the ACE III.

2.2.4 Behavioural data analyses

Rotated principal component analysis (rPCA), a dimensionality reduction technique, was adopted to cluster the above-mentioned 13 cognitive measures into related domains, reducing the number of multiple comparisons between the cognitive tests (Jolliffe & Cadima,

2016). This step maximized the power to investigate the impact of risk factors on cognition and brain–behaviour relationships. rPCA was conducted by using the *psych* package (Version 2.0.12) in R software (https://www.r-project.org/), following steps as: (1) *Preprocessing*. Listwise deletion procedure was used to deal with the missing data. Only participants who had no missing observations were kept (N = 208 at baseline; N = 176 at follow-up). (2) *Component extraction and estimation*. Principal component analysis was used to extract a smaller number of components that capture the most variance of the initial variables, representing the common cognitive processes underlying the 13 original cognitive measures. Scree plots and parallel analysis were used to determine the number of components (Horn, 1965). Parallel analysis generated a set of random correlation matrices (n = 500) by using the same number of variables (n = 13) and participants (N = 208 at baseline; N = 176 at follow-up). Then, I compared the solution to the random simulated normal data. The eigenvalues obtained from the actual matrix were compared with those obtained from the randomly generated matrices, and the estimated number of components was determined by selecting components with eigenvalues larger than 95th percentile of the randomly generated components' eigenvalues (for details, see also Appendix A). (3) *Rotation*. To examine the component structure among the initial variables, an orthogonal rotation method Varimax that constrains the components to be uncorrelated, was applied to the coefficient matrix (Kaiser, 1958). (4) *Component coefficients*. Component coefficients (*r*), reflecting the correlation between each of the components and each of the original variables, were thus obtained. Given the sample size in this study (N > 200), component coefficients that were larger than 0.4 were deemed practically significant (Hair Jr. et al., 1998; Stevens, 1992). (5) *Component scores*. Component scores were calculated by a regression method where the regression weights were found from the inverse of the correlation matrix times the coefficient of each variable on the corresponding components. The coefficients were used to interpret the components, and component scores were used for

the following analyses. (6) *Component similarities*. Components were extracted at the baseline and follow-up, respectively. To test the similarity of components extracted at each study session, to be capturing similar cognitive functions, Tucker's congruence coefficient was calculated (Lorenzo-Seva & ten Berge, 2006). In subsequent analyses, I used these cognitive components, rather than the individual tests to measure the impact of risk factors on cognition and brain–behaviour relationships.

2.2.5 MRI data acquisition and processing

Imaging data were obtained as part of a multimodal examinations in a 3T Siemens Verio MRI scanner and with 32-channel head coil (https://preventdementia.co.uk/for-researchers/). Resting-state fMRI data were acquired with T2*-weighted echo-planar imaging (EPI) sequence. 330 volumes were acquired, and each volume contained 35 slices (interleaved acquisition), with slice thickness of 3 mm (repetition time (TR) = 2000ms, echo time (TE) = 30ms, flip angle (FA) = 80^{o}, Field of View (FOV) = 192 × 192mm^{2}, voxel size = 3 mm^{3} isotropic). A 3D T1-weighted magnetization prepared rapid gradient-echo image (MPRAGE, 160 slices, voxel size = 1 mm^{3} isotropic, TR = 2300ms, TE = 2.98ms, FOV = 240 × 256mm^{2}, FA = 9^{o}) was also acquired. All scans were repeated after approximately two years on the same scanner using the same protocol.

Standard preprocessing procedures for resting-state fMRI data were performed with SPM12 (Statistical Parametric Mapping, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the AA pipeline software (Cusack et al., 2015) implemented in MATLAB R2019a (The MathWorks, United States). I discarded the first 5 volumes to allow for adaptation to the environment and equilibrium of the MR signal. In this pipeline (Figure 2.1a), I performed slice timing correction, motion correction, co-registration of functional and structural images,

normalization into standard MNI space, and spatial smoothing. Spatial normalization was performed using SPM12's segment-and-normalize procedure, whereby the T1 structural was segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) and normalized to a segmented MNI-152 template. These normalization parameters were then applied to all EPIs. The quality of spatial normalization was visually inspected for each participant and no participants showed a normalization failure. The data were then smoothed with a Gaussian kernel of 6mm full width at half maximum. I also applied a general linear model (GLM) that includes 24 head motion parameters – 6 rigid-body motion parameters, the first-order temporal derivative of them and quadratic terms of the original parameters and their derivatives (Satterthwaite et al., 2013) – and averaged signals from WM and CSF as covariates to reduce any residual effects of head motion and physiological noise. Lastly, all preprocessed data were temporally band-pass filtered (0.01-0.08 Hz) to remove low-frequency drift and high-frequency physiological noise (Salvador et al., 2008; Zuo et al., 2010).

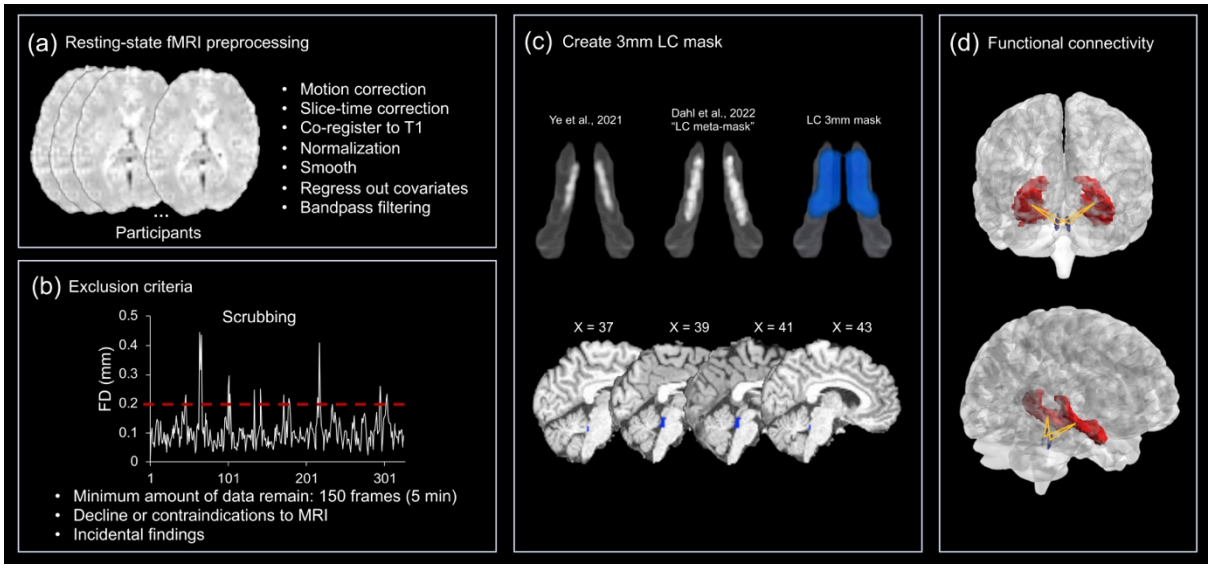

Figure 2.1 The flowchart of functional magnetic resonance imaging (fMRI) data processing. (a) The standard preprocessing pipeline for fMRI data. (b) Three exclusion criteria were used to exclude participants. A 'scrubbing' procedure was used to account for the effect of head movement on functional connectivity analyses (Power et al., 2012). (c) The top panel shows the study-specific 3mm locus coeruleus (LC) mask (in blue), which closely matched the 7T probabilistic atlas developed by Ye et al. (2021) and the LC meta-mask developed by Dahl et al. (2022). The bottom panel shows the study-specific mask superimposed on a participant's T1w structural data in MNI space. (d) Functional connectivity was calculated between the bilateral LC (in blue) and the hippocampus (in red). The hippocampus was defined with the automated anatomical labelling (AAL) atlas.

Because brain signal from the brainstem is susceptible to head movements, I performed careful measurement and control for head motion, by using a "scrubbing" procedure (Power et al., 2012). I first calculated an index of data quality called framewise displacement (FD) (for details, please also see Appendix A), which measures how much the head has changed position from one frame to the next, and can therefore be used to flag

frames of suspect quality based on the threshold of FD > 0.2 mm, in order to remove motion-contaminated data before calculating functional connectivity (Power et al., 2012). A participant inclusion criterion was then set to ensure a minimum amount of data remained after scrubbing, i.e., at least 150 frames (~5 min) of data (Figure 2.1b), based on wide agreement that ~5 min of fMRI data is an adequate for resting state functional connectivity analyses (Van Dijk et al., 2010). After completing the scrubbing procedure, the included participants had 74.2% ± 14.8% frames at baseline and 73.5% ± 15.0% at follow-up. Finally, I calculated the mean FD across the remaining good frames, which was further regressed in the group-level analyses (Power et al., 2014). After carefully censoring the motion-contaminated data, I found no significant difference in mean FD between APOE ε4 carriers and non-carriers at either baseline (t = 1.13, p = 0.26) or follow-up (t = 1.40, p = 0.17), nor between FHD+ and FHD- at either time point (baseline: t = -0.39, p = 0.70; follow-up: t = 0.51, p = 0.61). There was also no significant correlation between mean FD and CAIDE at either baseline (r = 0.07, p = 0.44) or follow-up (r = 0.08, p = 0.43). Furthermore, mean FD was not significantly associated with LC–Hippocampus functional connectivity at either time point (baseline: r = 0.001, p = 0.99; follow-up: r = 0.04, p = 0.72). These results suggest that head movement did not significantly influence the main results. The fMRI-based exclusion criteria are also illustrated in Figure 2.1b.

2.2.6 Regions of Interests (ROIs)

To ensure high accuracy in the localization of the LC, a binary LC mask of 3 mm^3 isotropic voxel size was created to closely match two previously published LC maps (Dahl et al., 2022; Ye et al., 2021), which were developed in the standard MNI space with 0.5 mm^3 isotropic voxel size. In order to achieve the highest precision, instead of resampling the LC maps to

match the fMRI data's voxel size (3 mm^3) using automatic scripts, a 3 mm^3 binary LC mask was manually drawn in MNI space with reference to the two LC maps. This is because the automatic scripts did not perform well when resampling the two referenced LC maps from high to low resolution due to the small size of these two LC regions of interest. The FSL software (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) was used for the drawing process, by following the same procedure as in Plini et al. (2021). The two 0.5 mm^3 LC maps were superimposed on a blank 3 mm^3 template in standard MNI space. The drawing process was then performed on this blank template by adding or removing voxels to include different anatomical locations of the two referenced maps without crossing the dorsal and medial raphe nuclei, as defined by Beliveau et al. (2015), and the cerebellar vermis white matter. At the end of this procedure, the new bilateral LC mask was symmetrical and consisted of 16 3 mm^3 voxels, was anatomically inclusive of the 7T LC map (Ye et al., 2021) and the LC meta-map (Dahl et al., 2022), and did not encroach on other pontine nuclei (Figure 2.1c).

The hippocampus was defined based on the automated anatomical labelling (AAL) atlas (Figure 2.1d). The functional connectivity (FC) between the LC and the hippocampus was derived using Pearson's correlation coefficient (*r*) on the denoised time courses (Figure 2.1d). The *r* value was then transformed to z value using Fisher's *r*-to-*z* transformation to improve normality for further statistical analysis. To avoid the formation of artificial anti-correlations (Anderson et al., 2011; Murphy et al., 2009), I did not perform global signal regression.

2.2.7 Hippocampus volume

In an independent study (Dounavi et al., 2022), T1-weighted MPRAGE of this cohort were corrected for field inhomogeneities using the Advanced Normalisation Toolbox (ANTs) N4 algorithm (Tustison et al., 2010) and processed using Freesurfer version 7.1.0 (Desikan et

al., 2006). The recon-all pipeline was run for every participant with standard settings. The brain masks and surfaces were inspected following recon-all, and manual corrections were applied: (a) in the form of erosion of non-brain voxels from the brain mask or non-WM voxels from the WM mask, (b) in the form of filling of areas where the brain was not correctly identified, or (c) with the addition of control points in cases where white matter was not successfully identified. Finally, the volume of the hippocampus (HCV) was derived for each participant at baseline and follow-up and included as a covariate for functional connectivity analyses.

2.2.8 Statistical approach

All statistical analyses were performed in R software. The normality of the data was assessed by combining the visualization of a quantile-quantile plot and the Shapiro–Wilk test. Demographic and clinical information of the study cohort was analysed across risk groups using chi-square (χ^2 tests) for categorical variables and Mann Whitney U tests for continuous (discrete) variables, given that they were not normally distributed in this cohort.

To investigate the cross-sectional effects of risk factors (APOE ε4 genotype and FHD) on cognition and functional connectivity, I used multiple linear regression models. Age, sex and years of education were included as covariates for cognition models, and mean FD and HCV values were additionally included as covariates for models of functional connectivity. The effects of APOE ε4 and CAIDE risk factors were modelled independently to avoid modelling the variance associated with APOE ε4 genotype in the same model twice. Spearman correlation analyses were used to assess the associations between cognition and CAIDE score given the non-normal distribution of CAIDE in this cohort. For any observed risk effect on cross-sectional changes of cognition or functional connectivity, interactions

between risk factors and the LC–Hippocampus functional connectivity on cognition were assessed through multiple regression models with the cognition as the dependent variable, the LC–Hippocampus FC, risk factors and the risk × FC interaction as independent variables, and age, sex, years of education, and HCV as covariates. For any observed interactions, I plotted the regression of LC–Hippocampus FC on cognitive performance for each level/value of the risk factor, to interpret the effect (Aiken & West, 1991). All continuous variables in the interaction terms, e.g., CAIDE and FC, in the moderation models were mean-centred (subtracting each the mean from each value) to avoid multicollinearity.

Longitudinal changes were first assessed for the entire cohort using random intercept linear mixed effect models (Cnaan et al., 1997). Specifically, I evaluated longitudinal changes of cognition (Eq. 1) and functional connectivity (Eq. 2) over two years using the following two equations.

$$Cognition_{jt} = \beta_0 + \beta_1\left(Time_{jt}\right) + u_j + r_{jt} \qquad (1)$$

$$FC_{jt} = \beta_0 + \beta_1\left(Mean\ FD_{jt}\right) + \beta_2\left(HCV_{jt}\right) + \beta_3\left(Time_{jt}\right) + u_j + r_{jt} \qquad (2)$$

For each participant *j*, measures of cognition/functional connectivity at each time point *t* served as dependent variables, and the timepoint (a categorical variable with two levels: baseline and follow-up) served as the independent variable. Mean FD and HCV at each time point *t* were included as covariates for the functional connectivity model only (Eq. 2). u_j represented individual variability in the intercepts, i.e., a random effect.

The presence of a longitudinal change for the entire cohort was then further assessed to determine whether it varied in relation to the risk factors, as assessed by the interaction term ($Risk_j \times Time_{jt}$). Age at baseline, sex, and years of education, were included as covariates for the cognition models (Eq. 3), and mean FD and HCV were additionally included as covariates for the functional connectivity models (Eq. 4). For the CAIDE model, I did not control for the age, sex, and education as they are included in the CAIDE score.

$$Cognition_{jt} = \beta_0 + \beta_1(Age_j) + \beta_2(Sex_j) + \beta_3(Education_j) + \beta_4(Risk_j) + \beta_5(Time_{jt}) + \beta_6(Risk_j \times Time_{jt}) + u_j + r_{jt} \quad (3)$$

$$FC_{jt} = \beta_0 + \beta_1(Age_j) + \beta_2(Sex_j) + \beta_3(Education_j) + \beta_4(Mean\ FD_{jt}) + \beta_5(HCV_{jt}) + \beta_6(Risk_j) + \beta_7(Time_{jt}) + \beta_8(Risk_j \times Time_{jt}) + u_j + r_{jt} \quad (4)$$

Lastly, the presence of risk-related longitudinal change in cognition or functional connectivity was further investigated to determine whether risk factors influence brain-cognition association longitudinally. Multiple linear regression modelling was used with change scores (i.e., follow-up - baseline) in cognition as the dependent variable, and a risk factor, changes in FC, and their interaction as independent variables. Baseline age, sex, years of education, and changes in HCV were included as covariates.

Although the baseline and follow-up datasets were not independent, I considered each in its own right, in addition to testing for longitudinal changes in cognition and functional connectivity. During the two years, a proportion of the participants may have brain changes that are yet subthreshold to clinical manifestations, or that may not yet manifest as longitudinal changes.

2.2.9 Additional analyses

I also performed an additional analysis to test whether the inclusion of APOE ε2ε4 carriers would confound the main results. Details are given in Appendix A.

2.3 Results

2.3.1 Demographic characteristics

Demographic characteristics of the cohort at baseline and follow-up, stratified by APOE ε4 genotype and FHD, are shown in Table 2.1. There were no significant differences in age, sex, or years of education between the groups. APOE ε4 allele genotype was more frequently found in the FHD+ than FHD- group at baseline ($p = 0.01$) and follow-up ($p = 0.02$). CAIDE scores (including APOE status) were significantly higher for the FHD+ than FHD- group at baseline ($p = 0.03$) and follow-up ($p = 0.003$). Naturally, CAIDE scores including APOE status were significantly higher for the APOE ε4+ than APOE ε4- group at baseline ($p = 0.0003$) and follow-up ($p = 0.0002$), but when APOE status was excluded, the CAIDE scores did not differ between the two groups (Table 2.1).

Table 2.1 Demographic characteristics of the cohort at baseline and follow-up based on the dementia family history and on APOE genotype

	Baseline			Follow-up		
	FHD- (n=107)	FHD+ (n=103)	*p* (Mann-Whitney U)	FHD- (n=89)	FHD+ (n=99)	*p* (Mann-Whitney U)
Age (y)	52.0 ± 11.0	53.0 ± 7.0	0.52	54.0 ± 10.0	55.0 ± 6.0	0.22
Years of Education	16.0 ± 5.0	16.0 ± 5.0	0.34	17.0 ± 5.0	16.0 ± 5.0	0.21
CAIDE (incl. APOE status)	5.0 ± 4.0 (n=107)	6.0 ± 2.0 (n=101)	0.03	6.0 ± 4.0 (n=89)	7.0 ± 3.0 (n=93)	0.003
			p (Chi-Square)			*p* (Chi-Square)
Sex (%female)	69.2%	71.8%	0.67	69.7%	71.7%	0.76
APOE ε4 (% Carriers)	28.0% (n=107)	44.6% (n=101)	0.01	28.1% (n=89)	44.3% (n=97)	0.02
	APOE ε4- (n=133)	APOE ε4+ (n=75)	*p* (Mann-Whitney U)	APOE ε4- (n=118)	APOE ε4+ (n=68)	*p* (Mann-Whitney U)
Age (y)	53.0 ± 8.0	52.0 ± 8.0	0.06	55.0 ± 8.0	54.5 ± 8.0	0.08
Years of Education	16.0 ± 5.0	17.0 ± 4.5	0.51	16.0 ± 4.8	17.0 ± 5.0	0.47
CAIDE (incl. APOE status)	5.0 ± 3.0 (n=133)	7.0 ± 3.0 (n=75)	0.0003	6.0 ± 3.0 (n=118)	7.0 ± 4.0 (n=64)	0.0002
CAIDE (excl. APOE status)	5.0 ± 2.0 (n=133)	4.0 ± 3.0 (n=75)	0.12	5.0 ± 2.0 (n=118)	4.5 ± 3.0 (n=64)	0.25
			p (Chi-Square)			*p* (Chi-Square)
Sex (%female)	69.9%	70.7%	0.91	71.2%	69.1%	0.77

Note: median ± interquartile range (IQR) was reported for continuous variables. Abbreviations: FHD+/-, Family history of dementia positive/ negative; APOE ε4+/-, Apolipoprotein ε4 genotype positive/ negative; CAIDE, Cardiovascular Risk Factors, Aging and Incidence of Dementia.

2.3.2 Cognitive domains

I first performed parallel analyses and plotted scree plots to determine the number of components that best represented the original 13 cognitive measures at baseline and follow-up, separately. Results showed that the eigenvalues of the first three components were larger than 95th percentile of the randomly generated eigenvalues at both study timepoints (Figure 2.2a), which indicated that the three-component (C) solution best represented the data. The three components were then rotated to be uncorrelated with each other, and could cumulatively explain a total of 41% percentage of the variance, at baseline (C1 = 17%; C2 = 13%; C3 = 12%) and 40% at follow-up (C1 = 17%; C2 = 12%; C3 = 11%) (Figure 2.2b).

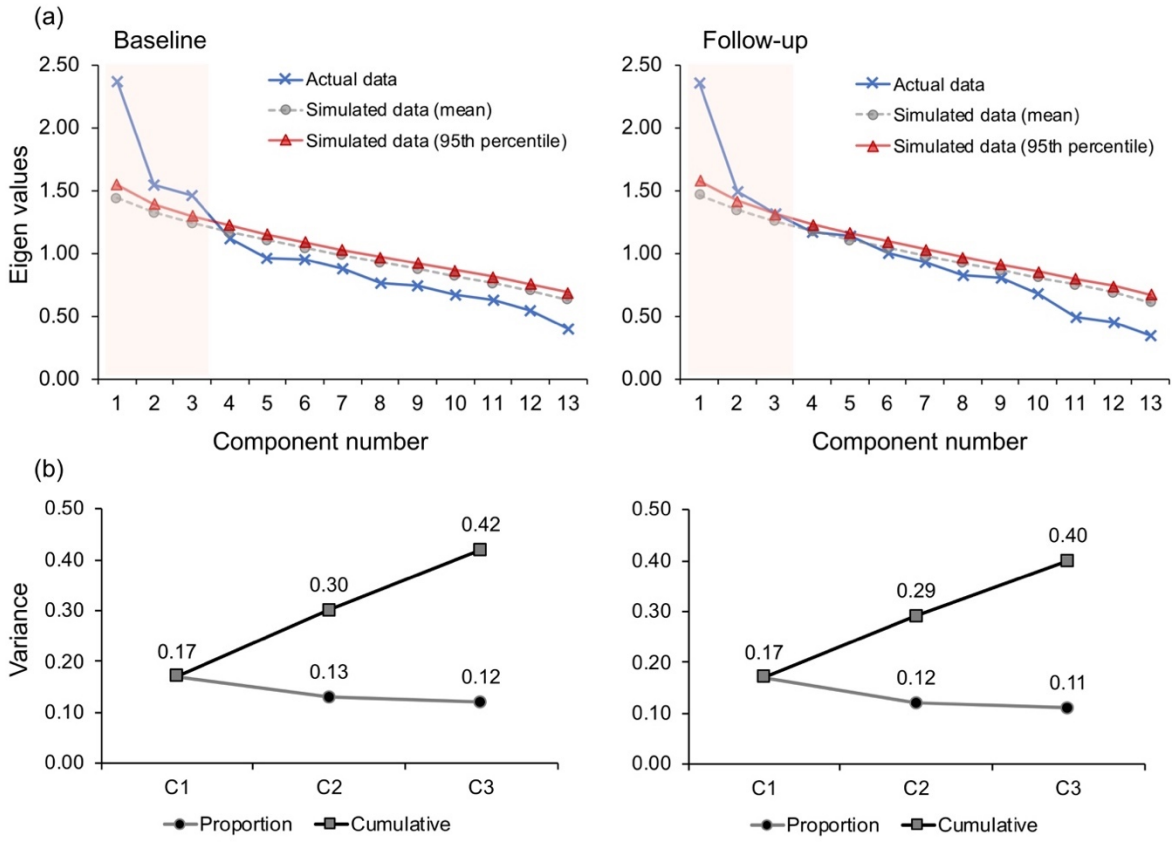

Figure 2.2 Data reduction of cognitive information. (a) Scree plots and parallel analysis for the baseline and follow-up datasets. Eigenvalues of the principal components obtained from the actual data (in blue line) were compared to those of random simulated data (mean values in grey line and 95th percentile in red line). Eigenvalues larger than 95th percentile of the randomly generated 500 eigenvalues (simulation) determined the number of components. (b) The three extracted components were rotated to be uncorrelated with each other. The proportion of variance explained by each component, and the cumulative variance explained by the three are presented for the baseline and follow-up datasets. Abbreviations: C1, component 1; C2, component 2; C3, component 3.

The loading values (weights) of the cognitive measures (Figure 2.3a) reflect the relationships between the original measures and the corresponding components. Measures with higher coefficients were more closely related to the components. Based on the cognitive functions that the highest loading measures tapped into (for details, see Table 6.2), in subsequent analyses, I refer to: C1 as 'episodic and relational memory'; C2 as 'working and short-term (single-feature) memory'; C3 as 'verbal, visuospatial functions, and short-term (conjunctive) memory' (for details see Appendix A).

The highest loading measures and their coefficients for each component differed for the baseline and follow-up data. For example, verbal functions, visuospatial functions, and short-term (conjunctive) memory were strongly loaded on the third component at baseline. At follow-up, implicit memory rather than short-term memory was loaded on the third component (Figure 2.3a). I found high similarity between baseline and follow-up for C1 (ϕ = 0.90), and C3 (ϕ = 0.76), with relatively low similarly for C2 (ϕ = 0.40) (Figure 2.3b).

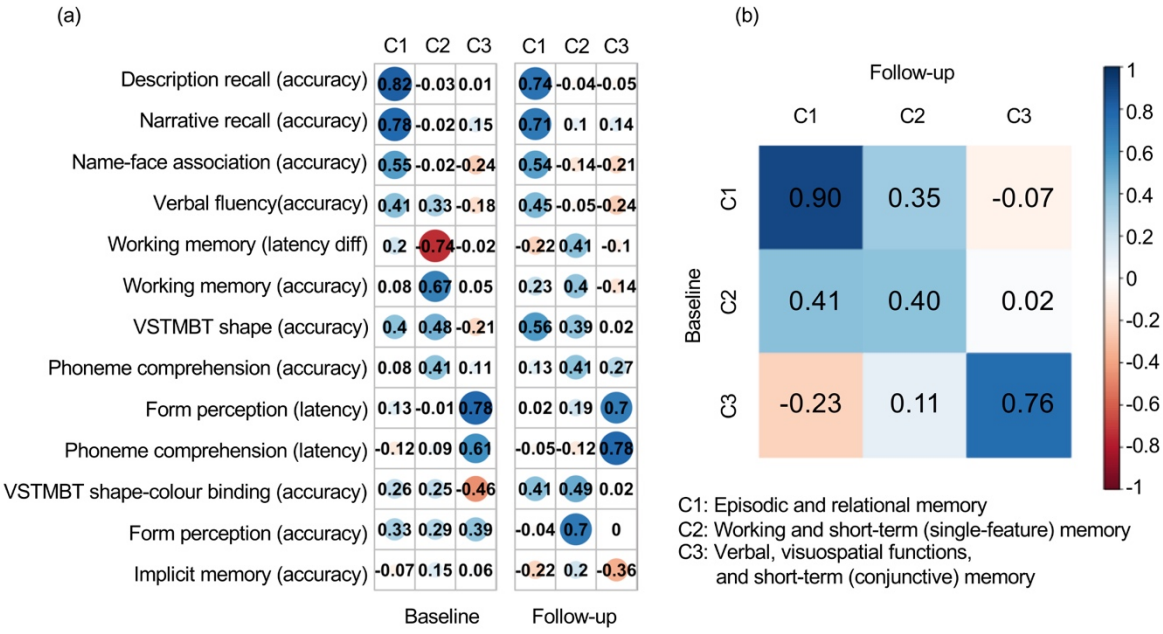

Figure 2.3 Interpretation of data-derived cognitive domains. Component (C) coefficients and Tucker's congruence coefficients between baseline and follow-up are shown. (a) The coefficients for 13 original cognitive measures (in rows) on the three components (in columns). A larger absolute coefficient (darker colours and larger solid circles) represents a closer relationship between the cognitive measure and the corresponding component. Cool/warm colours represent the positive/negative relationships between cognitive measures and components. (b) Similarities among the components across baseline (in rows) and follow-up (in columns) were measured by Tucker's congruence coefficients. The diagonal values represented the similarities for each of the components with itself across time, and off-diagonal values indicated the similarities for each of the components with the other two components across time. Cool/warm colours represent the positive/negative relationships with darker colours representing correlation magnitude, as shown in the colour-bar scale. Abbreviations: VSTMBT, visual short-term memory binding test; diff, difference.

2.3.3 Impact of risk factors on cognition

Episodic and relational memory

At baseline, the multiple linear regression model showed a significant positive association between episodic and relational memory and APOE ε4 allele [β (*SE*) = 0.28 (0.13), $p < 0.05$] (Figure 2.4a), independent of sex, age and years of education (Table 2.2). At follow-up, there was a trend effect of the APOE ε4 allele [β (*SE*) = 0.27 (0.15), $p = 0.07$] (Figure 2.4b). Education was significantly positively associated with episodic and relational memory at baseline [β (*SE*) = 0.09 (0.02), $p < 0.0001$] and follow-up [β (*SE*) = 0.10 (0.02), $p < 0.0001$].

Table 2.2 Statistical summary of the multiple regression model testing the relationship between APOE and episodic and relational memory

Model summary		Baseline			Follow-up		
		R^2	$F_{(4, 201)}$	*p*	R^2	$F_{(4, 169)}$	*p*
		0.16	9.55	<0.0001	0.17	8.48	<0.0001
DV	IV	β	*se*	*p*	β	*se*	*p*
Episodic and relational memory	APOE ε4	0.28	0.13	0.04	0.27	0.15	0.07
	Age	-0.02	0.01	0.17	-0.008	0.01	0.55
	Sex	0.27	0.14	0.06	0.25	0.16	0.11
	Years of education	0.09	0.02	<0.0001	0.10	0.02	<0.0001

Note: unstandardized coefficient (β) and standard error (se) are reported. DV, dependent variable; IV, independent variable; APOE ε4, Apolipoprotein ε4 genotype.

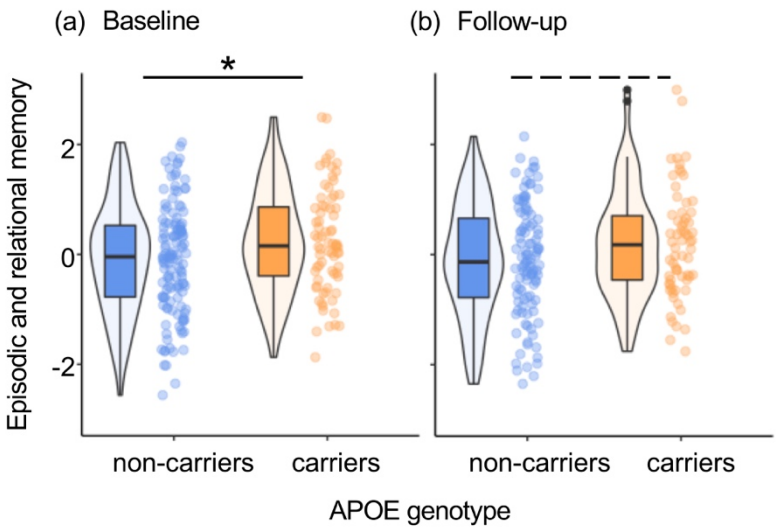

*Figure 2.4 The effect of APOE genotype on episodic and relational memory at (a) baseline and at (b) follow-up. * = p<0.05. The dashed line represents a trend effect (p = 0.07).*

The multiple linear regression models showed no associations between FHD and episodic and relational memory, at either timepoint. Spearman correlation analyses showed no significant associations between the CAIDE score and episodic and relational memory, at either timepoints.

Working and short-term (single-feature) memory

I found no associations between APOE ε4, FHD, or CAIDE score with working and short-term (single-feature) memory. Education was significantly positively associated with performance in this domain, independent of the other factors, at baseline [β (*SE*) = 0.04 (0.02), $p < 0.05$] only.

Verbal, visuospatial functions, and short-term (conjunctive) memory

I found no associations between APOE ε4 or FHD with verbal, visuospatial functions, and short-term (conjunctive) memory. Age was significantly negatively associated with performance in this domain, independent of the other factors, at baseline [β (*SE*) = -0.04 (0.01), $p < 0.005$]. The CAIDE score was significantly associated with verbal, visuospatial functions, and short-term (conjunctive) memory at baseline (*rho* = -0.17, $p < 0.05$, Figure 2.5a), and at follow-up (*rho* = -0.20, $p < 0.05$, Figure 2.5b). Higher CAIDE scores were significantly associated with poorer performance.

Finally, there was no significant longitudinal change of cognition in any of the three cognitive domains over two years.

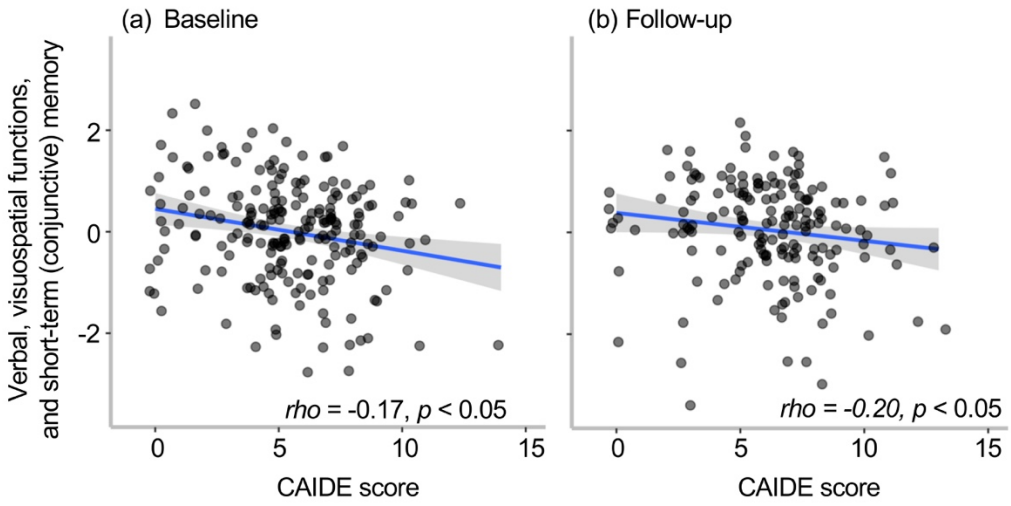

Figure 2.5 The associations between the CAIDE dementia risk score and verbal, visuospatial functions, and short-term (conjunctive) memory at (a) baseline and at (b) follow-up. Abbreviation: CAIDE, Cardiovascular risk factor, Aging, and Incidence of Dementia.

2.3.4 Longitudinal change of LC–Hippocampus functional connectivity

I found a significant negative association between time and the LC–Hippocampus functional connectivity [β (*SE*) = -0.07 (0.03), $p < 0.05$], after controlling for mean FD and HCV (Table 2.3), indicating reduced connectivity at two-years follow-up relative to baseline across the whole cohort (Figure 2.6).

Table 2.3 Statistical summary of longitudinal linear mixed effect model testing for longitudinal change in the LC–Hippocampus functional connectivity

DV	IV	*β*	*se*	*p*
LC–Hippocampus connectivity	Time	-0.07	0.03	0.02
	mean FD	-0.03	1.47	0.98
	Hippocampal volume	0.04	0.06	0.50

Note: unstandardized coefficient (β) and standard error (se) are reported. DV, dependent variable; IV, independent variable; FD, framewise displacement; LC, Locus Coeruleus

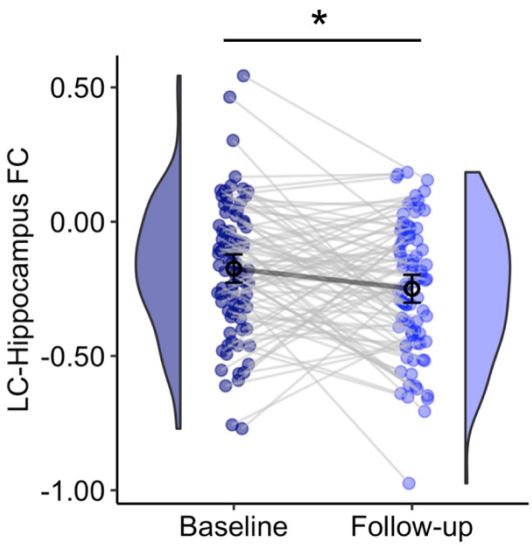

*Figure 2.6 Longitudinal decline of the LC–Hippocampus FC over two years in cognitively healthy middle-aged adults. * = p<0.05. Abbreviations: LC, Locus Coeruleus; FC, functional connectivity.*

2.3.5 Impact of risk factors on the LC–Hippocampus functional connectivity and brain–behaviour relationships

There were no significant associations between APOE ε4, FHD, or CAIDE scores and LC–Hippocampus functional connectivity, cross-sectionally, or longitudinally (for details, see Appendix A, Tables 6.3-6.8).

At baseline, none of the risk factors moderated the relationship between functional connectivity and cognition. At follow-up, the multiple linear regression model with CAIDE,

LC–Hippocampus FC, and CAIDE × LC–Hippocampus FC interaction term as independent variables, and verbal, visuospatial functions, and short-term (conjunctive) memory as the dependent variable showed a significant negative association between the interaction term (CAIDE × LC–Hippocampus FC) and verbal, visuospatial functions, and short-term (conjunctive) memory [β (*SE*) = -0.44 (0.21), $p < 0.05$] (Table 2.4). I then plotted the association between LC–Hippocampus FC and cognition at three levels of CAIDE, i.e., mean and ± 1 standard deviation (SD), to interpret this interaction effect. In individuals with low (– 1 SD) or high (+ 1 SD) CAIDE scores, higher functional connectivity was associated with better or worse cognition, respectively (Figure 2.7).

Table 2.4 Regression coefficients of the model testing the relationship between CAIDE, LC–Hippocampus and verbal, visuospatial functions, and short-term (conjunctive) memory

Model summary		Baseline			Follow-up		
		R^2	$F_{(4, 122)}$	*p*	R^2	$F_{(4, 77)}$	*p*
		0.07	2.47	0.05	0.06	1.16	0.34
DV	IV	β	*se*	*p*	β	*se*	*p*
Verbal, visuospatial functions, and short-term (conjunctive) memory	CAIDE	-0.09	0.03	0.006	-0.03	0.05	0.59
	LC–HC	-0.09	0.33	0.79	0.30	0.53	0.57
	CAIDE × LC–HC	-0.15	0.13	0.25	-0.44	0.21	0.04
	Hippocampal volume	-2.17e-04	2.27e-04	0.34	4.99e-05	3.30e-04	0.88

Note: unstandardized coefficient (β) and standard error (se) are reported. CAIDE and LC-HC have been centred in this model. DV, dependent variable; IV, independent variable; CAIDE, Cardiovascular risk factors, Ageing and the Incidence of Dementia; LC–HC, Locus Coeruleus–Hippocampus functional connectivity.

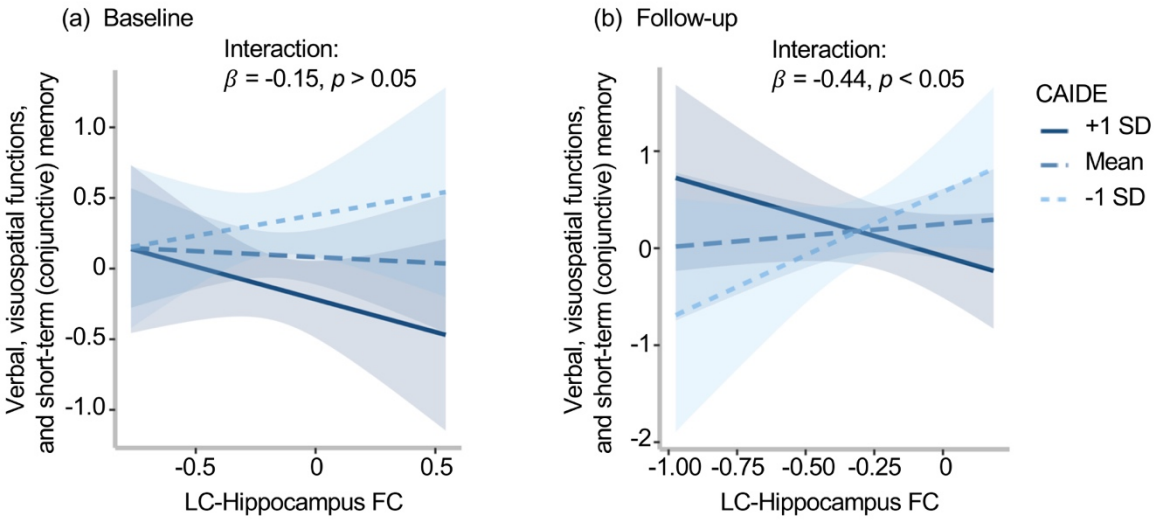

Figure 2.7 The CAIDE score significantly moderated the brain–behaviour relationship. The relationship was plotted at the fixed values of CAIDE (mean and ± 1 SD) to show the effect of CAIDE at (a) baseline and (b) follow-up. The LC–Hippocampus functional connectivity and the verbal, visuospatial functions, and short-term (conjunctive) memory were positively associated for individuals with low CAIDE score, and negatively associated for those with high scores, at (b) follow-up, but not baseline (a). Abbreviations: LC, locus coeruleus; CAIDE, Cardiovascular risk factor, Aging, and Incidence of Dementia; FC, functional connectivity; SD, standard deviation.

2.4 Discussion

It is well acknowledged that AD pathological processes start decades before clinical manifestations, but the brain mechanism of sporadic AD and its interactions with risk factors in midlife remain unclear. I examined whether risk factors for late-life AD were associated with cognition, functional connectivity between two key structures in AD pathophysiology (the LC and the hippocampus), and the brain-behaviour relationship between the two, cross-

sectionally and longitudinally in a cohort of middle-aged and cognitively healthy individuals. For the first time, I found that APOE ε4 genotype was significantly associated with episodic and relational memory, and that CAIDE scores were significantly associated with verbal, visuospatial functions, and short-term (conjunctive) memory functions in this cohort. I found no association between risk factors and the LC–Hippocampus functional connectivity. However, for the first time, I found that the CAIDE score significantly moderated the relationship between cognition and the LC–Hippocampus functional connectivity. These novel results shed light on some of the earliest brain–behaviour alterations associated with the risk of future AD in cognitively healthy individuals cross-sectionally. I found no longitudinal effects of risk factors on cognition, LC–Hippocampus functional connectivity, or their relationship, but I did observe a significant longitudinal decline of LC–Hippocampus FC over two years for the entire cohort. The lack of more prominent longitudinal effects of risk factors is likely due to the narrow follow-up time window (2 years) in this relatively young midlife cohort, an estimated 23 years from dementia onset (Dounavi et al., 2022).

The APOE ε4 allele was significantly associated with better cognition in episodic and relational memory at baseline and follow-up (trend), independent of sex, age and years of education. Previous research has suggested that the APOE ε4 allele, although being associated with poorer health outcomes in old age, may have a positive effect earlier in life. For example, it has been associated with better visual perception (Ritchie et al., 2017), short-term memory (Zokaei et al., 2020), higher intelligence quotient, and more economical use of memory-related neural resources in young healthy humans (Mondadori et al., 2007). The better performance in young/middle-aged APOE ε4 carriers may underlie a compensatory response, which, in the presence of incipient AD-related pathology, supports more efficient cognitive performance (Cacciaglia et al., 2022). These results may also be interpreted based on the antagonistic pleiotropy hypothesis of aging (Williams, 1957), which proposes that

deleterious genes, such as the APOE ε4 gene allele, have survived through evolution because they might confer an advantage early in life, when humans are reproductively fit. To the best of my knowledge, these results are the first to report an impact of genetic risk for late-life AD in cognitively healthy middle-aged individuals on episodic memory, the hallmark cognitive dysfunction in early clinical dementia and mild cognitive impairment (Irish et al., 2011). Thus, they highlight the importance of studying the origins of Alzheimer's disease in this age group, over 20 years before typical symptom onset.

I found that higher CAIDE scores were significantly associated with worse cognition in verbal, visuospatial functions, and short-term (conjunctive) memory, both at baseline and at follow-up. Previous studies from the same cohort have reported significant negative associations of CAIDE scores with visuospatial functions and navigational abilities (Ritchie et al., 2018; Ritchie et al., 2017). I did not observe a longitudinal effect, similarly to other studies of this cohort (Dounavi et al., 2021; Low et al., 2021), possibly due to the relatively young age and the short follow-up window (Ritchie et al., 2018; Ritchie et al., 2017). I caution that the interpretability of the effect of risk on each individual function is limited by their composite assessment in this study and requires individuation in future studies with a longer longitudinal follow-up window.

I found that LC–Hippocampus functional connectivity decreased significantly over two years. The previously reported effect of age on LC–Hippocampus functional connectivity is inconsistent, possibly due to different age ranges used in different studies. In healthy young and early midlife adults (age range: 18–49), LC functional connectivity to the parahippocampus was negatively associated with age (Zhang et al., 2016). However, another study of a lifespan adult cohort (age range: 19-74) found no association of age with the LC–Hippocampus/parahippocampus functional connectivity (Jacobs et al., 2018). In a broader age-range lifespan cohort (age range: 8–83), Song et al. (2021) found a positive quadratic

age effect (u-shape) on LC–parahippocampal functional connectivity, suggesting an increased interaction between these two regions in children and older adults. Therefore, the finding from this study advances the literature, by showing that the LC–Hippocampus functional connectivity decreases with age in midlife.

Alternatively, this result could be explained by overall changes in functional connectivity across the brain over time, or by changes in the scanner. To address this, I tested for overall changes in functional connectivity over 2 years. Specifically, I defined 214 brain regions based on a published brain map (Power et al., 2011), calculated the mean functional connectivity between them at each time point (see Chapter 3, Section 3.2.4 for details), and compared the differences in mean connectivity between baseline and follow-up. No significant longitudinal changes in overall functional connectivity were observed in this cohort. In addition, the baseline and follow-up data were obtained from a single site - Imperial College London - where the same scanner was used to acquire the imaging data. Therefore, this result is unlikely to be driven by overall functional connectivity or the scanner differences.

Another key question in this study was to examine whether risk factors impact LC–Hippocampus functional connectivity and its role in cognition. For the first time, I found that CAIDE score significantly moderated this brain-behaviour relationship. Stronger LC–Hippocampus functional connectivity was associated with better cognition for individuals with low CAIDE scores, and with worse cognition in those with high scores. The presence of this effect in the follow-up, but not the baseline dataset is likely due to the older age of the cohort at follow-up. Previous studies in older adults found that stronger LC–Hippocampus functional connectivity was significantly associated with better cognition (Jacobs et al., 2015). The finding from this study advances understanding by suggesting that

the connectivity between the LC and the hippocampus supports cognition in midlife individuals who have low dementia risk scores.

Furthermore, the result suggests that, in the presence of high dementia risk scores, LC–hippocampus functional connectivity is negatively associated with cognition. Previous studies have shown that a high CAIDE score, of more than 12, confers a probability of 16.4% for future dementia, with scores above 8 associated with a probability of more than 4% (Kivipelto et al., 2006). In a study of middle-aged individuals with a mean age of 46, participants with a score greater than 8 had a 29% 40-year risk for dementia (Exalto et al., 2014). These findings suggest that a proportion of this present study's participants, who have a CAIDE score greater than 8, will develop dementia. Assuming that AD pathology is underway in this proportion of individuals with high dementia risk scores, the result from this study lends indirect support to the hypothesis that LC hyperactivity and associated hyper-connectivity initiates the spread of pathological tau to MTL (Weinshenker, 2018), and particularly the hippocampus, in the early stages of AD. The ensuing neurodegeneration may explain why hyper-connectivity is associated with worse performance in individuals with high dementia risk scores. However, the neural mechanisms of AD neuropathology genesis remain contested. Given the lack of tau biomarker status for this cohort, future studies that integrate tau and functional connectivity information are required to further test the proposal that tau spreads from the LC to the hippocampus via functional connectivity pathways. Furthermore, future studies from the continuing longitudinal follow-up of this cohort will validate the role and nature of these changes in individuals who display AD neuropathology as they get older.

I did not observe any significant effects of risk factors for AD on LC–Hippocampus connectivity. Previous studies on MCI and AD patients have shown disrupted or lower LC–Hippocampus functional connectivity (MCI: Jacobs et al. (2015), age: 65.1 ± 4.5 years;

Liebe et al. (2022), age: 73.3 ± 7.5 years; AD patients: Zhao et al. (2017)), compared to age-matched healthy controls. One previous study investigating cognitively healthy middle-aged adults with familial risk for late-onset dementia found no effect of AD risk on LC–Hippocampus connectivity (Del Cerro et al. (2020), age: 50.4 ± 8.3 years). Consistent with this previous study, the null result from the present study suggests that AD risk factors are not associated with the LC–Hippocampus connectivity in middle-aged individuals who are cognitively healthy.

In summary, the PREVENT-Dementia study is a longitudinal multi-site study targeted at identifying early biomarkers for Alzheimer's disease. In this study, I provide early proof that the recruited cohort, with a mean age of 52/54 years at baseline/follow-up, showed a disrupted role of LC–Hippocampus connectivity in cognition with an increasing CAIDE score. APOE ε4 genotype or FHD did not moderate this brain–behaviour relationship. In other words, when the genetic risk alone was considered, no alterations of brain–behaviour relationships were found. It was only when a risk score (CAIDE) incorporating genetic risk in combination with lifestyle factors, sex and age was considered, that such alterations were unravelled. Furthermore, I did not observe any effects of sex, and the moderation was maintained when age was additionally controlled for in the model. Taken together, these results provide strong evidence that brain–behaviour alterations in individuals with higher CAIDE scores may be driven by lifestyle risk factors included in this dementia risk score (i.e., blood pressure, cholesterol, physical activity, body mass index, years of education).

Hence, these findings highlight the importance of considering modifiable risk factors when stratifying risk populations, or potentially designing randomized control trials. Another work in this cohort has demonstrated that modifiable stimulating lifestyle factors affect cognition, particularly in individuals at high risk for late-life AD (for details, see Chapter 4), and lends further support to this idea. In fact, a randomized multi-domain control trial in the FINGER

population (mean age 70 years old) over two years demonstrated that the applied lifestyle and vascular interventions had an impact on cognition (Stephen et al., 2019). Hence, further investigation of pathological alterations in relation to modifiable risk factors in midlife is warranted to unveil the sequalae of brain and behaviour alterations leading to dementia. Strengths of this study are its large well-characterized middle-aged cohort. State-of-the-art analysis methods and a thorough quality control protocol were applied to the acquired data.

Methodological considerations

Limitations include the short follow-up window of the study and the absence of further well-established preclinical biomarkers such as amyloid and tau status. Female sex was overrepresented in the studied cohort, but no effect of biological sex was found on any of the variables of interest, suggesting that sex does not drive this study's findings. Standard MR functional sequences provide limited resolution of the diminutive LC volume, and thus, these results need to be confirmed by higher-resolution imaging that specifically targets the LC region in future studies.

3. Chapter 3: Genetic risk of dementia is associated with longitudinal loss of functional brain network segregation in cognitively healthy, middle-aged individuals

3.1 Introduction

In this chapter, I ask whether the intrinsic organisational properties of the brain have changed in a midlife cohort at risk of late-onset Alzheimer's disease (AD), using the resting-state fMRI technique. In particular, I assessed the segregation property of functional brain networks, as this is an emerging marker of brain health in both normal and pathological ageing.

The brain is composed of intrinsically wired functional networks (Crossley et al., 2013; Smith et al., 2009), each corresponding to a set of distinct and tightly connected regions (Cole et al., 2014; Smith et al., 2009), often involved in specialised functional processing (Sporns & Betzel, 2016; Wig, 2017). Such modular functional organisation of the brain in the form of distinct networks is critical for cognition (Achard et al., 2006; Bullmore & Sporns, 2012; Chan et al., 2014). For example, across the adult lifespan, individuals with greater segregation of functional brain networks show better long-term episodic memory (Chan et al., 2014). Therefore, disrupted network segregation may lead to cognitive and behavioural decline. In the following sections, I summarise factors and/or conditions associated with disruption of functional network segregation and its implications for cognition, including (a) age across the adult lifespan, (b) risk factors for late-onset AD in asymptomatic older adults, (c) mild cognitive impairment (MCI), and (4) Alzheimer's disease. Finally, I identify the remaining research gaps that will be addressed in this chapter.

(a) In healthy populations, increasing adult age is associated with reduced network segregation or more diffuse functional organisation of the brain (Chan et al., 2014; Wig, 2017). Such 'dedifferentiation' of functional networks is, in turn, associated with age-related decline in cognitive and motor function (Chan et al., 2014; King et al., 2018; Kong et al., 2020; Manza et al., 2020; Pedersen et al., 2021; Varangis et al., 2019). Conversely, preservation of network segregation is associated with maintenance of cognitive and motor function in healthy ageing (Cassady et al., 2020; Chan et al., 2021; Gallen et al., 2016) and in patients with brain injury (Arnemann et al., 2015), suggesting that functional network segregation supports cognitive reserve (Stern, 2012).

(b) In asymptomatic older adults (mean age > 65 years), loss of network segregation is associated with the accumulation of AD pathologies, such as beta-amyloid (Aβ) and tau (Brier et al., 2014; Ewers et al., 2021), or the presence of the APOE ε4 allele (Ng et al., 2018), compared to the absence of these conditions. These findings suggest that network segregation is impaired in cognitively unimpaired older adults at risk for AD. This reduction in network segregation in the high-risk group was further associated with cognitive decline (Ng et al., 2018), whereas maintenance of network segregation was associated with preserved cognitive performance, despite the presence of AD pathology (Ewers et al., 2021). (c) Furthermore, decreases in network segregation were also observed in patients with MCI (Farràs-Permanyer et al., 2019; Jiao et al., 2021) and AD (Dai et al., 2019; Ewers et al., 2021) compared to age-matched controls. (d) Importantly, an accelerated decline in network segregation with ageing was associated with increasing dementia severity (Chan et al., 2021), and maintenance of network segregation was associated with preserved cognition (Ewers et al., 2021). Taken together, the accumulating evidence points to network segregation as a marker of brain health in both normal and pathological ageing.

An important question that remains to be addressed is the selective vulnerability of

individual networks to loss of functional segregation. Studies suggest that large-scale brain systems undergo nonuniform changes during healthy ageing, with the associative system being more susceptible to age-related 'dedifferentiation' than the sensorimotor system (Betzel et al., 2014; Chan et al., 2014; Geerligs et al., 2015; Pedersen et al., 2021; Siman-Tov et al., 2017; Wig, 2017). However, it remains unclear which individual networks within the associative system are more liable to segregation loss during healthy ageing and in preclinical AD populations.

Furthermore, it remains unknown whether the risk of late-onset AD is associated with altered functional network segregation in cognitively healthy, middle-aged individuals, who may not develop symptoms for decades. Answering this question has important implications for identifying intermediate phenotypes of the earliest brain changes in the preclinical stages of AD (Foo et al., 2020), which will help to provide urgently needed early disease biomarkers in the earliest stages of the disease, and to determine the earliest time point for network segregation changes along the AD spectrum.

To address these two research gaps, the first aim of this study was to investigate age-related differences in functional segregation of individual networks in a large healthy adult lifespan cohort from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) open dataset (N = 652, 18-88 years). The second aim was to test hypotheses derived from the results of the healthy ageing investigation, to examine the impact of three risk factors for late-onset Alzheimer's disease (APOE ε4 allele, FHD and CAID scores) on network segregation in midlife. Cross-sectional and longitudinal (over 2 years) changes in network segregation and their associations with cognition were examined in the midlife cohort of cognitively healthy individuals from the PREVENT-Dementia research programme (N = 210) described in detail in Chapter 2.

My first prediction was that there would be differential age effects on ten predefined brain networks based on a comprehensive whole-brain atlas (Power et al., 2011) across the healthy adult lifespan (the Cam-CAN cohort), with high-order networks in particular expected to show the strongest age effect. The second prediction was that in the midlife PREVENT-Dementia cohort, the global segregation of functional networks, and the segregation of networks most susceptible to the healthy ageing processes would be influenced by the risk of late-onset AD. Furthermore, studies have shown that the DMN is particularly vulnerable to AD pathology (Greicius et al., 2004; Kucikova et al., 2021; Márquez & Yassa, 2019; Rombouts et al., 2005). For example, atrophy and metabolic abnormalities occur in the core regions of the DMN at early stages of AD progression (Buckner et al., 2005; Dickerson et al., 2009; Minoshima et al., 1997). Therefore, I expected that functional segregation of the DMN, in particular, would be affected by AD risk in the middle-aged cohort. Specifically, I tested three hypotheses in the midlife cohort: (i) reduced global network segregation in the high-risk groups compared to the low-risk group cross-sectionally, (ii) a greater reduction in high-order networks, particularly in the DMN, and (iii) a more pronounced longitudinal decline over two years in the high-risk group compared to the low-risk group.

3.2 Methods

3.2.1 Participants

Healthy lifespan adults

The healthy lifespan cohort was drawn from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) research programme (http://www.cam-can.org/), a large-scale collaborative research project aimed at elucidating the neurocognitive mechanisms that

underpin healthy cognitive ageing. A detailed protocol has been described elsewhere (Shafto et al., 2014). Ethical approval was obtained from the Cambridgeshire 2 (now East of England-Cambridge Central) Research Ethics Committee, and informed consent was obtained from all participants prior to assessments and imaging. The cohort consisted of healthy volunteers aged 18-88 years. I examined data collected in the second phase of this project. 652 participants (322 male; 330 female) underwent structural and resting-state fMRI scans. All participants have fMRI data, and 646/652 have structural MRI data after quality control.

Middle-aged adults at risk for late-life AD

See Chapter 2, Section 2.2.1 for a full description of the cohort. In this chapter, I have included different subsets of participants from the previous chapter, tailored to the specific analyses of brain network organisation.

Exclusion of participants. At baseline, 17 participants were excluded due to lack of participation or contraindications to MRI, 6 due to incidental findings, and 20 due to inadequate brain coverage (for details, please see the following section on the *functional brain network construction*). At follow-up, 19 participants were excluded due to decline or contraindications to MRI, 3 due to incidental findings, and 1 due to inadequate brain coverage. In addition, 21 participants were further excluded from the longitudinal analyses, due to missing either the baseline or the follow-up sessions. Therefore, the dataset for the cross-sectional analyses (i.e., baseline session) was N = 167, and the dataset for the longitudinal analyses (i.e., remaining at both baseline and follow-up sessions) was N = 144 (Figure 3.1).

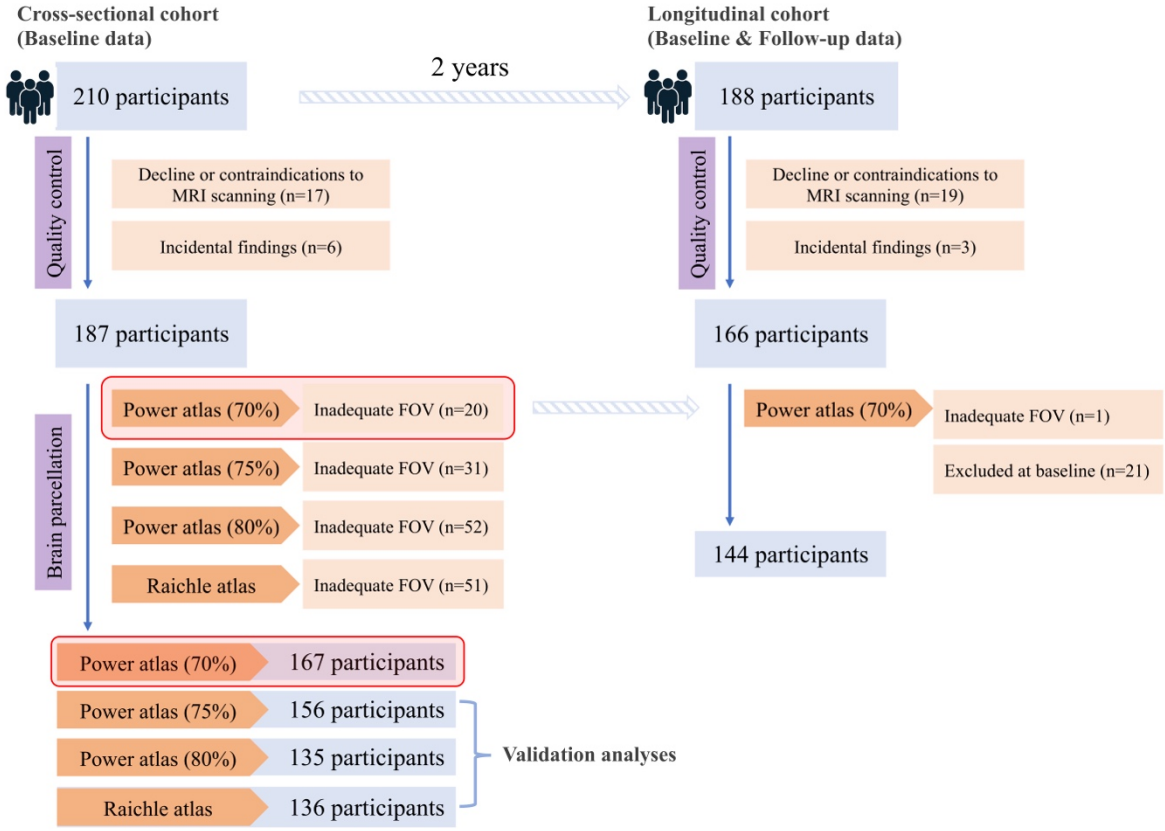

Figure 3.1 Participant exclusions for resting-state fMRI data analyses of the PREVENT-Dementia cohort. Two brain parcellation schemes were adopted to define the nodes of the brain networks: Power atlas (Power et al., 2011) and Raichle atlas (Raichle, 2011). Due to inadequate field of view (FOV) for Power atlas, I excluded participants with less than 70% of the initial brain nodes (node = 214). To test if the results were driven by a particular subset of participants, I also tested two more stringent thresholds: 75% and 80%. Due to inadequate FOV for Raichle atlas, I excluded participants without full coverage of the whole brain nodes (node = 33).

3.2.2 Assessments from the PREVENT-Dementia study

See Chapter 2 for full descriptions of the assessments used in this study, including the three risk factors (APOE ε4 allele, FHD, and the CAIDE score) in Section 2.2.2 and three

cognitive domains: (i) episodic and relational memory, (ii) working and short-term (single-feature) memory, and (iii) verbal, visuospatial functions, and short-term (conjunctive) memory in Section 2.2.3, Section 2.2.4, and Section 2.3.2.

3.2.3 MRI data acquisition and pre-processing

The Cam-CAN study

Imaging data were collected at a single site (MRI-CBSU) using a 3T Siemens TIM Trio scanner with a 32-channel head coil. Full descriptions of the MRI protocols have been described elsewhere (Taylor et al., 2017). Resting-state fMRI data were acquired using a T2*-weighted echo planar imaging (EPI) sequence with participants resting with their eyes closed. 261 volumes were acquired, and each volume contained 32 axial slices (in descending order) with a slice thickness of 3.7 mm and an interslice gap of 20% [repetition time (TR) = 1970 ms, echo time (TE) = 30 ms, flip angle (FA) = 78°, field of view (FOV) = 192 × 192 mm^2, voxel size = 3 mm × 3 mm × 4.44 mm]. A 3D T1-weighted magnetization prepared rapid gradient-echo image (MPRAGE, TR = 2250 ms, TE = 2.99 ms, FA = 9°, FOV = 256mm × 240mm × 192mm, voxel size = 1 mm^3 isotropic) was also acquired.

Resting-state fMRI data were preprocessed by the Cam-CAN group using a standard preprocessing pipeline with statistical parametric mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and automatic analysis (AA) software (Cusack et al., 2015). Details of the pipeline are described in Taylor et al. (2017). Briefly, raw fMRI data were unwarped using field map images for distortion correction due to magnetic field inhomogeneities, realigned for motion correction, and corrected for slice timing. Functional images were then coregistered with T1 structural images and normalised to Montreal Neurological Institute (MNI) standard space using normalisation parameters

derived from the Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) procedure (Ashburner, 2007). To further account for the effects of head motion, a wavelet despiking method was applied to remove motion artefacts (Patel et al., 2014).

In addition, I applied a general linear model (GLM) including 24 head motion parameters and white matter (WM) and cerebrospinal fluid (CSF) signals to reduce residual effects of head motion and other noise confounders. The 24 parameters included six original rigid-body motion parameters, the first-order temporal derivatives of these six parameters, and 12 quadratic terms of the original motion parameters and their derivatives (Satterthwaite et al., 2013). Framewise displacement (FD) motion parameters (Power et al., 2012) were calculated as the sum of the absolute values of the differentiated realignment estimates at each time point (see Appendix A for full descriptions and formula), which measures the movement of the head from one volume to the next (Power et al., 2012). I then averaged the FD across time points and regressed it in the group-level analyses to further account for head movement. Finally, high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, corresponding to 100 s) was applied to remove low-frequency artefacts. Spatial smoothing was not applied for network analysis, as suggested by Alakörkkö et al. (2017).

Morphometric brain measures were derived from the T1 images using the Mindboggle pipeline (Klein et al., 2017). Grey matter volume (GMV) of 34 brain regions per hemisphere based on the Desikan-Killiany atlas (Desikan et al., 2006) was extracted using the underlying Freesurfer processing pipeline (Klein & Tourville, 2012). The mean GMV of these cortical areas was used in this study to represent the structural integrity.

The PREVENT-Dementia study

For details on acquisition parameters and pre-processing of MRI data, please refer to Chapter 2, Section 2.2.5. As the analyses in Chapter 2 were updated more recently, two pre-processing steps were not carried out in the current study: (i) regressing out the averaged signals from WM and CSF at the individual level; (ii) applying the scrubbing approach to strictly control the effect of head motion. I found no significant difference in mean FD between APOE ε4 carriers and non-carriers at either baseline ($t = 0.93$, $p = 0.36$) or follow-up ($t = 0.04$, $p = 0.97$), nor between FHD+ and FHD- at either time point (baseline: $t = 0.08$, $p = 0.93$; follow-up: $t = -0.90$, $p = 0.37$), suggesting that head movement did not significantly influence the main results, i.e., the effect of APOE ε4 genotype on functional segregation of brain networks. Although there were significant positive relationships between mean FD and CAIDE at both baseline ($r = 0.22$, $p = 0.004$) and follow-up ($r = 0.30$, $p = 0.0001$), CAIDE did not show significant associations with network segregation in this study.

3.2.4 Resting-state fMRI data analyses

Functional brain network construction

A graph-theoretic framework was adopted to guide analyses of the functional organisation of brain networks using resting-state fMRI data.

Node definition. 214 brain nodes (spherical, 5 mm diameter) were defined based on a previously published functional system map (Power et al., 2011) comprising 10 functional brain networks: Motor 1 (sensorimotor hand), Motor 2 (sensorimotor mouth), Visual, Auditory, default mode (DMN), frontal-parietal control (FPN), cingulo-opercular control (CON), ventral attention (VAN), dorsal attention (DAN) and salience network (SN).

The resting-state fMRI data from the PREVENT cohort have an insufficient field of view (FOV) to cover the whole brain, resulting in the exclusion of some brain nodes in this functional brain map (Power et al., 2011). In addition, different fMRI scan angles were set for different participants, resulting in different FOVs that prevented the exclusion of the same set of brain nodes for each participant. To overcome these limitations, I excluded different sets of brain nodes from this brain atlas based on participants' specific FOV and constructed individualised brain networks (Figure 3.2b, see also Appendix B for details).

To ensure that participants with poor brain coverage, leading to a small number of retained brain nodes, did not bias the network analyses, I excluded participants with less than 70% of the original 214 brain nodes. This threshold was chosen to retain a relatively good number of brain nodes and a satisfactory number of participants to ensure statistical power. The number of retained brain nodes was also included as a covariate in the statistical models to further account for its effect.

Edge definition. Functional connectivity (FC) between pairs of predefined brain nodes was obtained by calculating the Pearson correlation coefficient *r* of the denoised fMRI time courses derived from these nodes (van den Heuvel & Hulshoff Pol, 2010), forming the FC matrix (Figure 3.2d). To avoid the formation of artificial anticorrelations, I did not perform global signal regression (Anderson et al., 2011; Murphy et al., 2009). Negative connectivity was removed due to its ambiguous meaning (Chai et al., 2012; Murphy et al., 2009).

Thresholding the FC matrix to form a sparse matrix is important to remove spurious connections (van den Heuvel et al., 2017). FC matrices were, therefore, thresholded from 5% to 50% connection density with a 5% interval, as graphs become more random above a threshold of 50% (Humphries et al., 2006). The area under the curve (AUC) for the graph theoretical measure across all thresholds was calculated to provide a scalar that does not

depend on a specific threshold selection (Achard & Bullmore, 2007; Wang et al., 2009).

Participation coefficient

The participation coefficient (Pc) of a brain node represents the distribution of its connections across separate networks (Guimerà & Nunes Amaral, 2005; Power et al., 2013) and was therefore used to measure the segregation property of the functional brain network. The equation is as follows:

$$P_i = 1 - \sum_{m \in M} \left(\frac{k_i^w(m)}{k_i^w} \right)^2,$$

Where m is a network in a set of networks M. $k_i^w(m)$ is the weighted connections of node i with all nodes in the network m. k_i^w is the total weighted connections node i exhibits.

P_i close to 0 indicates that node i is highly segregated, with most of its connections restricted to its own network and a relatively sparse connections to other networks (Figure 3.2d). In contrast, P_i close to 1 indicates that node i is highly integrated with nodes of other networks, represented by more equally distributed connections among different networks (Figure 3.2d). To quantify the segregation of individual networks, I average P_i across brain nodes that were assigned to the same network. The average P_i of nodes across the whole brain was used to quantify global network segregation.

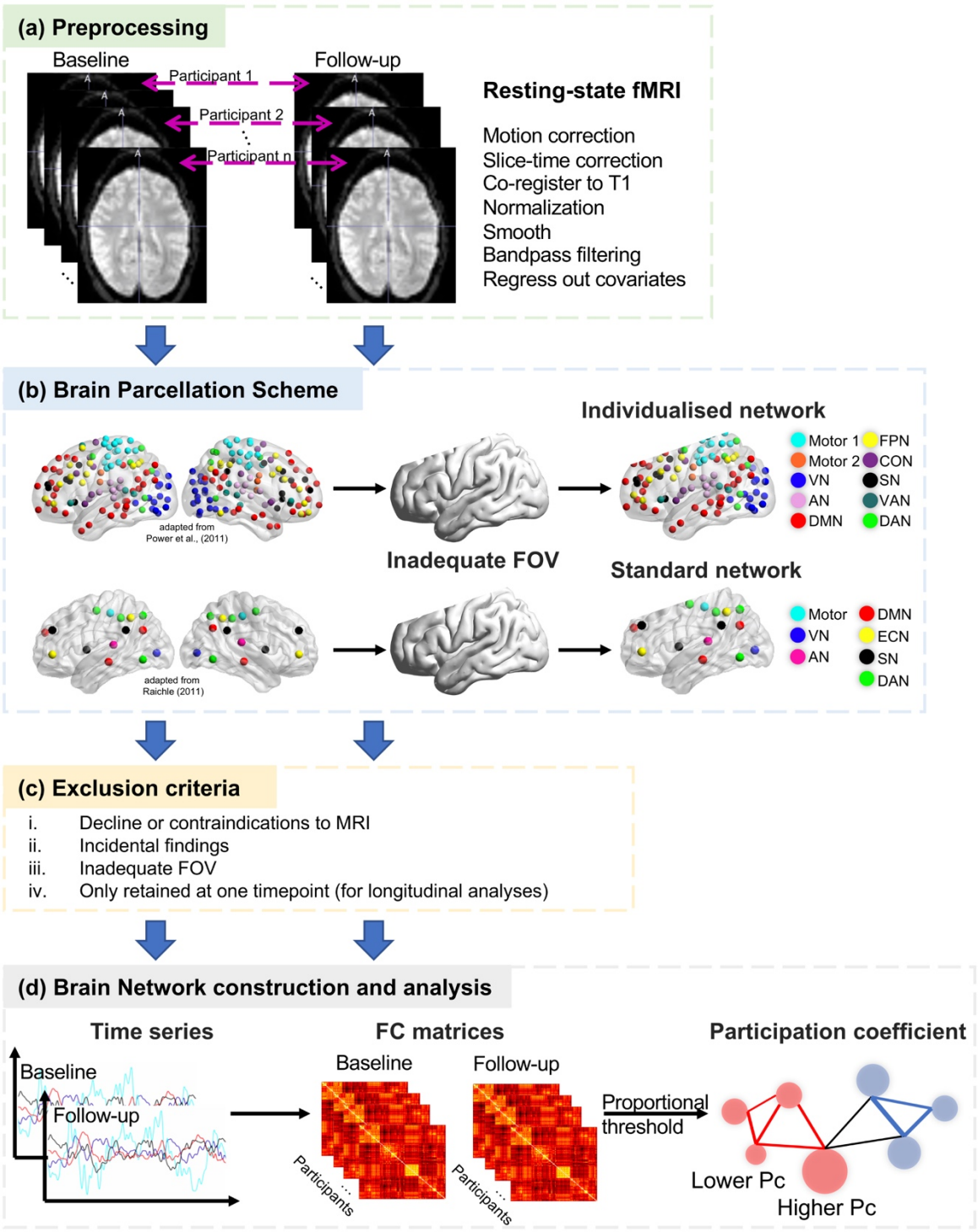

Figure 3.2 The schematic of the study design for the PREVENT-Dementia study. Resting-state fMRI data were collected from a cognitively healthy middle-aged cohort at baseline (N = 210; aged 40-59 years old), and some of them (N = 188) were followed up over two years. (a) Standard preprocessing steps were performed separately for the baseline and follow-up datasets. (b) Two brain parcellation schemes were adopted to define the nodes of the brain networks. Due to the inadequate field of view (FOV) and different scanning angles that were

set up for each participant's fMRI scan, individualised brain networks were adapted from a comprehensive brain atlas (Power et al., 2011), comprising 10 predefined networks, according to the coverage of individual-specific functional brain images. In addition, I adopted another brain parcellation scheme (Raichle, 2011) that comprises a smaller number of key regions for 7 predefined networks to validate the main results. In this atlas, I can ensure the same set of brain nodes for every participant. (c) Several criteria were applied to exclude the inappropriate data for the network analyses. (d) Time courses were extracted based on the brain nodes in the individual-specific atlas and correlated with each other to create functional connectivity (FC) matrices by using Pearson correlation (r). Proportional thresholds were applied to FC matrix to generate the sparse matrix for the calculation of participation coefficient (Pc) to describe functional segregation. The mock graph illustrates two different networks in red and blue. The node (in red) with lower Pc exhibits strong connections only within its belonging network (edges in red), but no connection to the other network (in blue), indicating higher functional segregation. By contrast, the node (in red) with higher Pc exhibits equally distributed connections to its belonging network (edges in red) and to the other network (edges in black), indicating lower functional segregation or a more diffused brain. Abbreviations: VN, visual; AN, auditory; DMN, default mode; FPN, frontal-parietal control; SN, salience; VAN, ventral attention; DAN, dorsal attention; CON, cingulo-opercular control; ECN, executive control.

3.2.5 Statistical analyses

The Cam-CAN study

All statistical analyses were performed using R software. The demographics of the participants are summarised in Table 3.1. I used multiple linear regression models to examine the relationship between global network segregation and mean cortical GMV, including age, sex, educational level, and mean FD as covariates. The ratio of mean cortical

GMV to intracranial volume was calculated for each participant to account for inter-individual differences in head size. To investigate the effect of age on global and individual functional network segregation, global and Pc of each of the ten networks were treated as dependent variables in separate models, with age as the independent variable and sex, education attainment, and mean FD as covariates. Multiple comparisons between the 10 individual networks were Bonferroni-corrected.

The PREVENT-Dementia study

The normality of the data was assessed by combining the visualization of a quantile-quantile plot and the Shapiro-Wilk test. Demographic and clinical information of this study cohort was analysed across risk groups, using χ^2 tests for categorical variables and Mann-Whitney U tests for continuous variables, given that they were not normally distributed in this cohort (Table 3.2).

Cross-sectional effects. Baseline data were used to examine cross-sectional effects. Multiple linear regression models were used to examine the associations of global and individual network Pc with risk factors (APOE ε4 genotype, FHD and CAIDE score), each in a separate model. Age, sex, years of education, mean FD, and number of brain nodes were included as covariates in all models. Multiple comparisons between the 10 individual networks were false discovery rate (FDR) corrected. Network Pc showing a significant risk effect was further assessed in relation to cognitive performance using multiple linear regression models controlling for age, sex, and years of education.

Longitudinal effects. Networks showing a cross-sectional change in the presence of a risk factor were also assessed for longitudinal change over two years. Specifically, mean FD and the number of brain nodes were first adjusted for network Pc at baseline and follow-up

separately. Change scores between the two study time points were then derived to evaluate longitudinal change. Multiple linear regression models were then applied with change scores in network Pc as the dependent variable and the risk factor as the independent variable, and age at baseline, sex, and years of education as covariates. Finally, for observed significant risk-related longitudinal changes in network segregation, I performed paired t-tests to see which risk groups showed significant changes in network Pc between baseline and follow-up. I also assessed the longitudinal relationship between network segregation and cognition using multiple linear regression models. Change scores in cognition were treated as the dependent variable, and change scores in network Pc as the independent variable, controlling for age at baseline, sex, and years of education.

3.2.6 Validation analyses for the PREVENT-Dementia study

Different participant exclusion criteria based on the brain coverage in the Power atlas

To assess the impact of the chosen node retention threshold of 70% for participant inclusion on the main results, I repeated the same analyses using two more stringent inclusion thresholds: 75% and 80%, or by excluding participants with less than 75% or 80% of the original brain nodes (node = 214) (Figure 3.1). The distribution of the number of remaining brain nodes in each network across the three thresholds is shown in Figure 7.1 in Appendix B.

Different parcellation schemes

To ensure that the individualised brain networks did not bias the network analyses, I used an alternative parcellation scheme (Figure 3.2b) that included a smaller number of key brain nodes (node = 33, spherical, 5 mm diameter) in 7 predefined brain networks (Raichle, 2011).

By using this parcellation scheme, I was able to retain all brain nodes and exclude participants without full coverage of these nodes, leading to a different subset of participants compared to the main analyses (based on the 70% node retention threshold in the Power atlas) (Figure 3.1).

3.3 Results

3.3.1 Demographic characteristics

The Cam-CAN cohort

Demographic specifications of the whole cohort are summarized in Table 3.1.

Table 3.1 Demographic information for the Cam-CAN cohort

		Whole cohort
Age range, y		18-88
Age (mean ± SD), y		54.4 ± 18.5
Sex (Female), %		50.61
Education [a]	University	395
	A Levels	68
	GCSE	111
	None	75

Note: [a] Education levels were categorized according to the British education system: 'none', no education over the age of 16 years; 'GCSE', General Certificate of Secondary Education; 'A Levels', General Certificate of Education Advanced Level; 'University', undergraduate or graduate degree. Educational information was missing for 3 participants. SD = standard deviation.

The PREVENT cohort

Demographic information of the cross-sectional and longitudinal cohorts after quality control of the fMRI data based on global network coverage (Figure 3.2b), stratified by APOE ε4 genotype, and family history of dementia, are shown in Table 3.2. There were no significant differences in age, sex, or years of education between the groups. The frequency of the APOE ε4 allele genotype did not differ significantly between the FHD+ and FHD- groups, either cross-sectionally or longitudinally. CAIDE scores were significantly higher in the FHD+ group than in the FHD- group both cross-sectionally (p = 0.006) and longitudinally (p = 0.004). Naturally, the CAIDE scores including APOE status were significantly higher for the APOE ε4+ group than for the APOE ε4- group, both cross-sectionally (p = 0.0007) and longitudinally (p = 0.0003) (Table 3.2).

Table 3.2 Demographic information for the PREVENT-Dementia cohort cross-sectionally (at baseline) and longitudinally (over 2 years), stratified by family history of dementia and APOE genotype

		Family history			APOE ε4 (2 missing data)		
		FHD+ (n=79)	FHD- (n=88)	*p* values	APOE ε4+ (n=59)	APOE ε4- (n=106)	*p* values
Cross-sectional (n=167)	Age, y	53.00 (6.00)	52.00 (11.25)	0.36	52.00 (7.50)	53.50 (9.00)	0.16
	Sex (Female), %	67.09%	70.45%	0.76	67.80%	68.87%	1.00
	Years of education	16.00 (5.00)	16.00 (4.25)	0.55	17.00 (5.00)	16.00 (5.00)	0.21
	APOE ε4 (carriers) %	44.16%	28.41%	0.05	-	-	-
	CAIDE	6.00 (3.00)	5.00 (4.00)	0.006	7.00 (3.00)	5.00 (2.75)	0.0007
		FHD+ (n=76)	FHD- (n=68)	*p* values	APOE ε4+ (n=54)	APOE ε4- (n=88)	*p* values
Longitudinal (n=144)	Age at baseline, y	53.00 (6.00)	52.00 (11.25)	0.31	52.00 (7.00)	54.00 (8.00)	0.17
	Sex (Female), %	67.11%	69.12%	0.94	66.67%	68.18%	0.99
	Years of education	16.00 (5.00)	17.00 (5.00)	0.16	17.00 (5.00)	16.00 (4.25)	0.64
	APOE ε4 (carriers) %	44.59%	30.88%	0.13	-	-	-
	CAIDE at baseline	6.00 (3.00)	5.00 (4.00)	0.004	7.00 (3.00)	5.00 (3.00)	0.0003

Note: Values shown are in median (interquartile range, IQR) where applicable. p values were obtained from Mann-Whitney tests for continuous variables and from chi-squared tests for categorical variables. Abbreviations: FHD+/-, family history of dementia positive/negative; APOE ε4 +/-, Apolipoprotein ε4 genotype positive/ negative. CADIE, Cardiovascular Risk Factors, Aging and Incidence of Dementia.

3.3.2 Functional network segregation across the healthy adult lifespan from the Cam-CAN study

I first examined the associations (i) between global network segregation and mean cortical GMV and (ii) between global network segregation and age across the adult lifespan, to establish the efficacy of the participation coefficient (Pc) as a metric of brain health.

The multiple linear regression models showed a significant negative association between global Pc and mean GMV (β = -0.14, p = 0.03, Figure 3.3b), independent of age, sex, educational attainment, and head motion (i.e., mean FD) (Table 3.3). Higher global Pc (lower network segregation) was significantly associated with smaller cortical GMV. There was also a significant positive association between global Pc and age (β = 0.27, p < 0.0001, Figure 3.3c), independent of sex, educational attainment, and mean FD (Table 3.3). Increasing adult age was significantly associated with increased global Pc (reduced network segregation). In addition, sex was significantly associated with global Pc (β = -0.16, p = 0.02). Females had significantly lower global Pc (higher segregation) than males.

Network segregation is positively associated with structural brain integrity, and negatively associated with age throughout adulthood, showing that it tracks structural markers of brain health. Therefore, these findings suggest that network segregation serves as a functional marker of brain health. In the next section, I conducted network-by-network analyses of age-related changes in functional segregation.

Table 3.3 Regression models assessing associations of global participation coefficient (Pc) with mean cortical grey matter volume (GMV) and with age, controlling for covariates

Dependent variables	Independent variables	*β*	95% CI	*t*	*p*
Global Pc	GMV	-0.14	[-0.27, -0.01]	-2.17	0.03
	Age	0.14	[0.01, 0.27]	2.12	0.03
	Sex	-0.13	[-0.27, 0.01]	-1.81	0.07
	Education	-0.07	[-0.14, 0.00]	-1.84	0.07
	Mean FD	0.23	[0.15, 0.31]	5.79	<0.0001
Global Pc	Age	0.27	[0.19, 0.34]	6.57	<0.0001
	Sex	-0.16	[-0.30, -0.03]	-2.33	0.02
	Education	-0.05	[-0.12, 0.03]	-1.28	0.20
	Mean FD	0.24	[0.16, 0.32]	6.10	<0.0001

Note: Standard coefficient β was reported. To account for inter-individual differences in head size, grey matter volume in the first model was normalised to intracranial volume. CI = confidence interval; FD = framewise displacement.

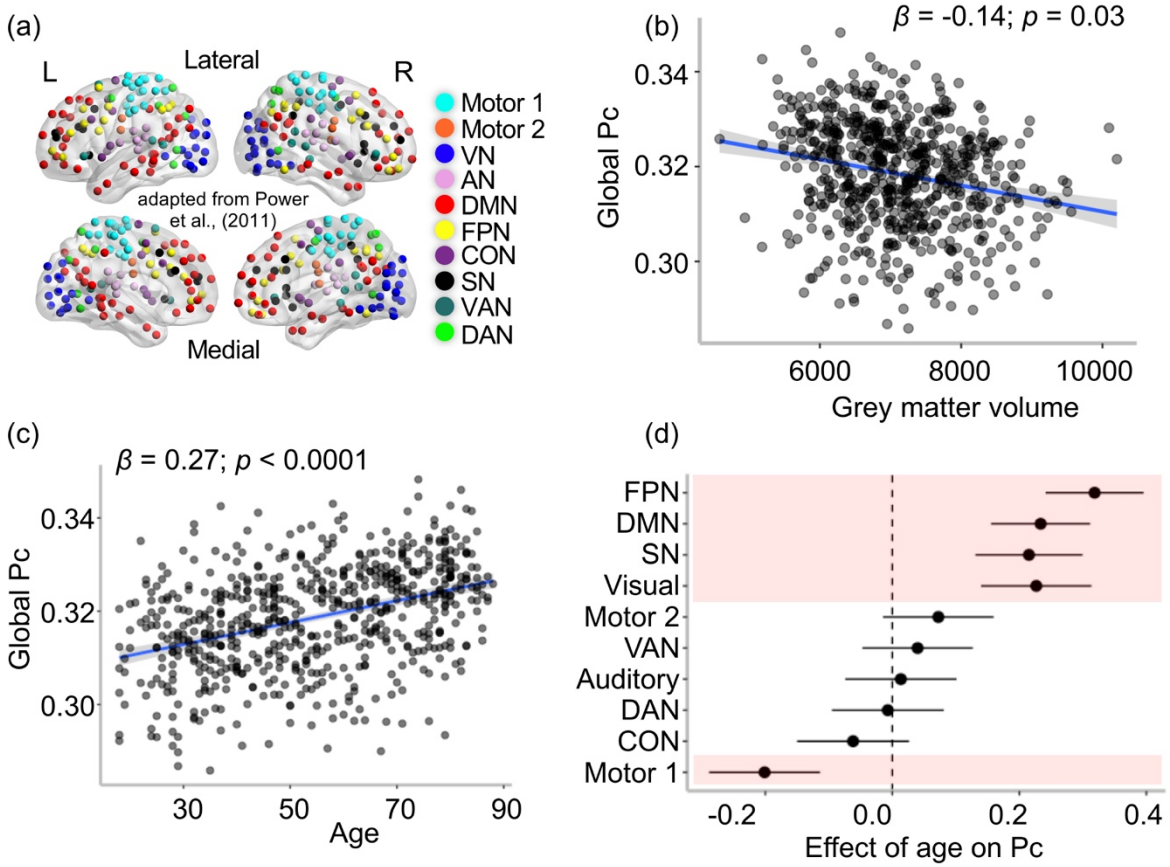

Figure 3.3 Associations between participant coefficient (Pc) with age and grey matter volume across the brain. (a) Ten comprehensive predefined networks based on Power et al. (2011). (b) Higher global Pc (loss of segregation) was significantly associated with smaller grey matter volume. (c) Higher global Pc (loss of segregation) was significantly associated with increasing age. (d) Network-specific effect of age on Pc. Standardized β coefficient (dot) and 95% confidence interval (CI, horizontal line) were shown for each network. Any CI encompasses zero (vertical dash line) represented non-significant results. Shading areas indicate significant results after Bonferroni correction across ten networks. Abbreviations: FPN, frontal-parietal control; SN, salience; DMN, default mode; VAN, ventral attention; DAN, dorsal attention; CON, cingulo-opercular control.

To investigate the selective vulnerability of individual networks to healthy ageing, I assessed the associations between Pc of each of the ten predefined brain networks (Figure 3.3a) and age. Pc of the DMN (β = 0.23, p < 0.0001), FPN (β = 0.32, p < 0.0001), SN (β = 0.22, p < 0.0001), and the Visual network (β = 0.23, p < 0.0001) were significantly positively associated with age (Figure 3.3d), independent of sex, education, and mean FD (Table 3.4), indicating significant age-related decreases in the segregation property of these networks. Conversely, I observed a significant negative association between Pc of the Motor 1 network and age (β = -0.20, p < 0.0001, Figure 3.3d), suggesting a significant age-related increase in functional segregation of this network. The other networks showed no significant associations with age (Table 3.4). All results reported here were Bonferroni corrected.

Table 3.4 Associations of network-specific participation coefficient (Pc) with age

	β	95% CI	*t*	*p*
Motor 1	-0.20	[-0.29, -0.11]	-4.52	<0.0001
Motor 2	0.07	[-0.01, 0.16]	1.63	1.00
Visual	0.23	[0.14, 0.31]	5.12	<0.0001
Auditory	0.01	[-0.07, 0.10]	0.30	1.00
Default mode	0.23	[0.16, 0.31]	5.87	<0.0001
Fronto-parietal	0.32	[0.24, 0.40]	8.11	<0.0001
Ventral attention	0.04	[-0.05, 0.13]	0.90	1.00
Cingulo-opercular	-0.06	[-0.15, 0.03]	-1.38	1.00
Dorsal attention	-0.01	[-0.10, 0.08]	-0.16	1.00
Salience	0.22	[0.13, 0.30]	5.00	<0.0001

Standard coefficient β was reported. All values reported here were adjusted for sex, education and mean framewise displacement. p values were Bonferroni corrected for multiple comparisons across ten networks. CI = confidence interval.

The results for the three higher-order networks (FPN, DMN, SN) were consistent with my hypothesis, based on prior literature. The networks involved in high-level cognitive processing showed the strongest age effects. However, the age effect on the functional segregation of the Motor 1 network was not predicted and added to the existing literature. In the following sections, I investigate the effects of risk factors for late-onset AD on network segregation in midlife both cross-sectionally and longitudinally, using the PREVENT-Dementia cohort.

3.3.3 Cross-sectional effects of AD risk factors on network segregation in midlife

I found a significant negative association between global Pc and APOE ε4 genotype at baseline (β = -0.44, p = 0.004), independent of age, sex, years of education, mean FD, and the number of brain nodes (Table 3.5). APOE ε4 carriers had significantly lower Pc (higher segregation) than ε4 non-carriers (Figure 3.4a). This result was further supported by validation analyses using different participant exclusion thresholds (75% and 80% retained nodes in the Power et al. (2011) atlas), and using a second brain parcellation scheme by Raichle (2011) (Table 7.1 in Appendix B). Neither family history of dementia nor the CAIDE score was significantly associated with global Pc at baseline, controlling for covariates (Table 7.2 in Appendix B).

Table 3.5 Associations between the main genetic risk factor for late-life Alzheimer's disease apolipoprotein ε4 (APOE ε4) allele and global participation coefficient (Pc) at baseline

Dependent variables	Independent variables	*β*	95% CI	*t*	*p*
Global Pc	APOE ε4	-0.44	[-0.74, -0.15]	-2.94	0.004
	Age	-0.06	[-0.20, 0.08]	-0.85	0.40
	Sex	0.003	[-0.30, 0.31]	0.02	0.99
	Years of education	0.05	[-0.09, 0.20]	0.73	0.47
	Mean FD	0.25	[0.11, 0.39]	3.44	0.001
	no. of brain nodes	0.27	[0.13, 0.41]	3.71	0.0003

Standard coefficient β was reported. CI = confidence interval. FD = framewise displacement.

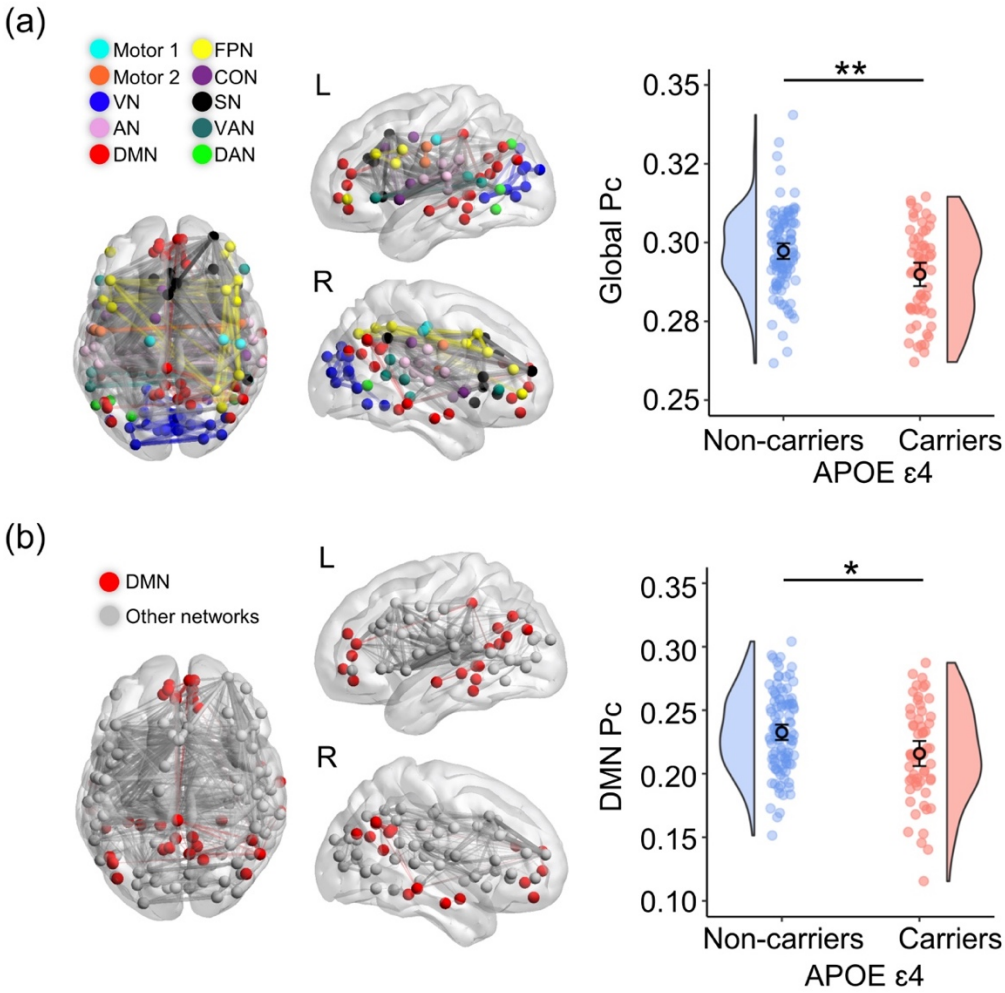

*Figure 3.4 Cross-sectional associations between APOE ε4 allele and participation coefficient (Pc) of functional brain networks. Brain nodes of 10 predefined networks retained for every participant were displayed (left panel) in a 3D glass brain just for visualization purposes. Coloured lines represent the functional connectivity within particular networks (e.g., red for DMN) and grey lines represent the between-network functional connectivity. (a) APOE ε4 carriers had lower global Pc (higher segregation) relative to non-carriers. (b) APOE ε4 carriers had lower Pc (higher segregation) of the default mode network (DMN) relative to non-carriers. Abbreviations: VN, visual; AN, auditory; DMN, default mode; FPN, frontal-parietal control; SN, salience; VAN, ventral attention; DAN, dorsal attention; CON, cingulo-opercular control. **p<0.005; *p<0.05, FDR corrected.*

I then assessed the effect of APOE ε4 genotype on the network-specific segregation cross-sectionally. Of the ten predefined networks (Power et al., 2011), only the DMN showed a significant negative association between APOE ε4 genotype and Pc at baseline (β = -0.48, p = 0.02, FDR correction), independent of age, sex, years of education, mean FD and number of brain nodes (Table 3.6). APOE ε4 carriers had significantly lower Pc (higher segregation) of the DMN than non-carriers (Figure 3.4b). This result was also supported by the validation analyses (Table 7.1 in Appendix B). Other networks did not show significant associations with APOE genotype (Table 3.6).

Table 3.6 Baseline differences in participation coefficient for 10 predefined networks (Power et al., 2011) between APOE ε4 carriers (+) and non-carriers (-)

Network	APOE ε4 +	APOE ε4 -	β	91% CI	p
Motor 1	0.35 ± 0.01	0.35 ± 0.01	0.13	[-0.20, 0.45]	0.77
Motor 2	0.33 ± 0.03	0.33 ± 0.03	-0.07	[-0.39, 0.26]	0.87
CON	0.33 ± 0.04	0.34 ± 0.03	-0.29	[-0.61, 0.04]	0.37
AN	0.35 ± 0.02	0.35 ± 0.02	0.08	[-0.25, 0.40]	0.87
DMN	0.22 ± 0.04	0.23 ± 0.03	-0.48	[-0.78, -0.18]	0.02
VN	0.29 ± 0.03	0.29 ± 0.03	0.12	[-0.20, 0.45]	0.77
FPN	0.28 ± 0.03	0.29 ± 0.03	-0.19	[-0.51, 0.14]	0.64
SN	0.31 ± 0.04	0.32 ± 0.03	-0.26	[-0.58, 0.06]	0.37
VAN	0.32 ± 0.03	0.32 ± 0.03	-0.04	[-0.36, 0.29]	0.90
DAN	0.33 ± 0.02	0.33 ± 0.02	-0.02	[-0.34, 0.30]	0.90

The shown values are mean ± standard deviation with the standardized coefficient (β) and 95% confidence interval (CI) from the linear regression models while controlling for age, sex, years of education, mean FD and the number of brain nodes. Abbreviations: AN, auditory; VN, visual; DMN, default mode; FPN, frontal-parietal control; VAN, ventral attention; CON, cingulo-opercular control; DAN, dorsal attention; SN, salience network. p values were FDR corrected.

3.3.4 Longitudinal effects of AD risk factors on network segregation in midlife

I assessed the associations of longitudinal changes in global and DMN segregation with APOE ε4 allele carriership. Before subtracting global and DMN Pc at follow-up from those at baseline, I first adjusted global and DMN Pc for mean FD and total number of brain nodes at each time point to correct for the effects of head movement and image quality. I found a trend positive association between APOE ε4 allele and longitudinal change in global Pc (β = 0.32, p = 0.06, Table 3.7), independent of baseline age, sex, years of education, mean FD, and the number of brain nodes. Paired t-tests showed no significant longitudinal change in global Pc for either APOE ε4 carriers or non-carriers (Figure 3.5a). There was a significant positive association between baseline age and longitudinal change in global Pc (β = 0.26, p = 0.002, Table 3.7). Older age at baseline was significantly associated with a greater longitudinal increase in global Pc (loss of network segregation) (Figure 3.6a).

Critically, I found a significant positive association between APOE ε4 genotype and longitudinal change in DMN Pc (β = 0.46, p = 0.008, Table 3.7), independent of baseline age, sex, years of education, mean FD, and the number of brain nodes. Paired t-tests showed that APOE ε4 carriers had a significant increase in DMN Pc (loss of network segregation) over two years (t = -2.80, p = 0.007, Figure 3.5b). However, APOE ε4 non-carriers did not show a significant longitudinal change. I also observed a significant positive association between the DMN Pc and baseline age (β = 0.19, p = 0.02, Table 3.7). Older age at baseline was significantly associated with a greater longitudinal increase in DMN Pc (loss of segregation) (Figure 3.6b).

Table 3.7 Longitudinal changes (over two years) in global and default mode network (DMN) participation coefficient in relation to apolipoprotein ε4 (APOE ε4) allele

Dependent variables	Independent variables	*β*	95% CI	*t*	*p*
Δ Global Pc	APOE ε4	0.32	[-0.01, 0.65]	1.90	0.06
	Age at baseline	0.26	[0.10, 0.43]	3.20	0.002
	Sex	0.13	[-0.21, 0.48]	0.76	0.45
	Years of education	-0.09	[-0.25, 0.07]	-1.08	0.28
Δ DMN Pc	APOE ε4	0.46	[0.12, 0.79]	2.70	0.008
	Age at baseline	0.19	[0.03, 0.36]	2.34	0.02
	Sex	0.20	[-0.15, 0.54]	1.12	0.26
	Years of education	-0.03	[-0.19, 0.13]	-0.37	0.71

Standard coefficient β was reported. CI = confidence interval. Δ = follow-up – baseline.

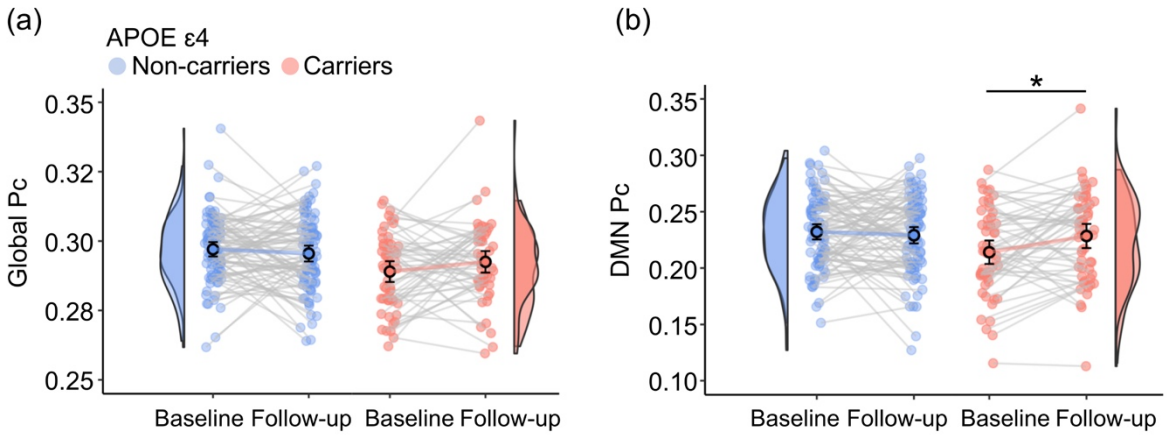

*Figure 3.5 Longitudinal associations between APOE ε4 allele and participation coefficient (Pc) of functional brain networks over two years. (a) No significant change in global Pc for either group. (b) APOE ε4 carriers only showed significantly increased Pc of the default mode network (DMN). *p<0.05, FDR corrected.*

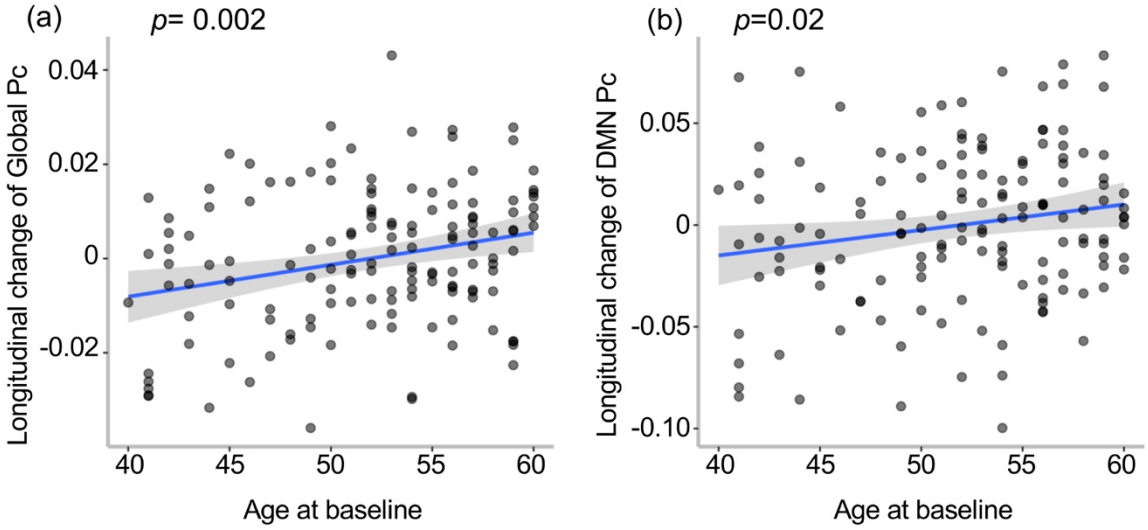

Figure 3.6 Associations between baseline age and longitudinal change of the participation coefficient (Pc). (a) increased age at baseline was associated with a longitudinal increase of the global Pc (loss of segregation). (b) increased age at baseline was associated with a longitudinal increase of the default mode network (DMN) Pc (loss of segregation).

3.3.5 Network segregation, cognition, and AD risk factors cross-sectionally and longitudinally

I tested the association between global and DMN segregation, and cognitive performance. Cross-sectionally, I found a significant negative association between global Pc and episodic and relational memory at baseline, independent of age, sex, and years of education (β = -0.19, p = 0.009). Higher global Pc (lower network segregation) was significantly associated with worse cognition (Figure 3.7a). The other two cognitive domains did not show significant relationships with global Pc (Table 3.8). In addition, higher Pc of the DMN (lower network segregation) was also significantly associated with worse episodic and

relational memory at baseline (β = -0.17, p = 0.02, Figure 3.7b), independent of age, sex, and years of education, but not the other two cognitive domains (Table 3.9). Longitudinally, there were no significant associations between the change scores in any of the three cognitive domains over the two years and the change scores in either the global Pc or the DMN Pc.

I then tested whether the observed cross-sectional association between global / DMN Pc and episodic and relational memory was moderated by APOE ε4 genotype. I found no significant interaction between APOE ε4 genotype and global / DMN Pc on cognition.

Table 3.8 Cross-sectional associations between global participation coefficient (Pc) and cognition in cognitively healthy middle-aged adults from the PREVENT-dementia study

Dependent variables	Independent variables	β	95% CI	t	p
Episodic and relational memory	Global Pc	-0.19	[-0.33, -0.05]	-2.64	0.009
	Age	-0.08	[-0.22, 0.06]	-1.12	0.27
	Sex	0.23	[-0.08, 0.54]	1.48	0.14
	Years of education	0.35	[0.20, 0.49]	4.81	<0.0001
Working and short-term (single-feature) memory	Global Pc	0.08	[-0.07, 0.23]	1.02	0.31
	Age	-0.06	[-0.21, 0.10]	-0.73	0.46
	Sex	-0.25	[-0.58, 0.08]	-1.47	0.14
	Years of education	0.15	[0.00, 0.30]	1.91	0.06
Verbal, visuospatial functions, and short-term (conjunctive) memory	Global Pc	-0.06	[-0.21, 0.09]	-0.81	0.42
	Age	-0.20	[-0.35, -0.05]	-2.56	0.01
	Sex	0.18	[-0.14, 0.51]	1.11	0.27
	Years of education	-0.01	[-0.16, 0.14]	-0.14	0.89

Note: Standard coefficient β was reported. CI = confidence interval.

Table 3.9 Cross-sectional associations between default mode network (DMN) participation coefficient (Pc) and cognition in cognitively healthy middle-aged adults from the PREVENT-dementia study

Dependent variables	Independent variables	*β*	95% CI	*t*	*p*
Episodic and relational memory	DMN Pc	-0.17	[-0.32, -0.03]	-2.33	0.02
	Age	-0.10	[-0.24, 0.05]	-1.35	0.18
	Sex	0.17	[-0.14, 0.48]	1.07	0.29
	Years of education	0.33	[0.19, 0.47]	4.56	<0.0001
Working and short-term (single-feature) memory	DMN Pc	0.08	[-0.08, 0.24]	1.00	0.32
	Age	-0.05	[-0.20, 0.11]	-0.61	0.54
	Sex	-0.22	[-0.55, 0.12]	-1.28	0.20
	Years of education	0.16	[0.00, 0.31]	2.00	0.05
Verbal, visuospatial functions, and short-term (conjunctive) memory	DMN Pc	-0.12	[-0.28, 0.03]	-1.55	0.12
	Age	-0.21	[-0.37, -0.06]	-2.76	0.007
	Sex	0.14	[-0.19, 0.47]	0.83	0.41
	Years of education	-0.02	[-0.17, 0.13]	-0.26	0.80

Note: Standard coefficient β was reported. CI = confidence interval.

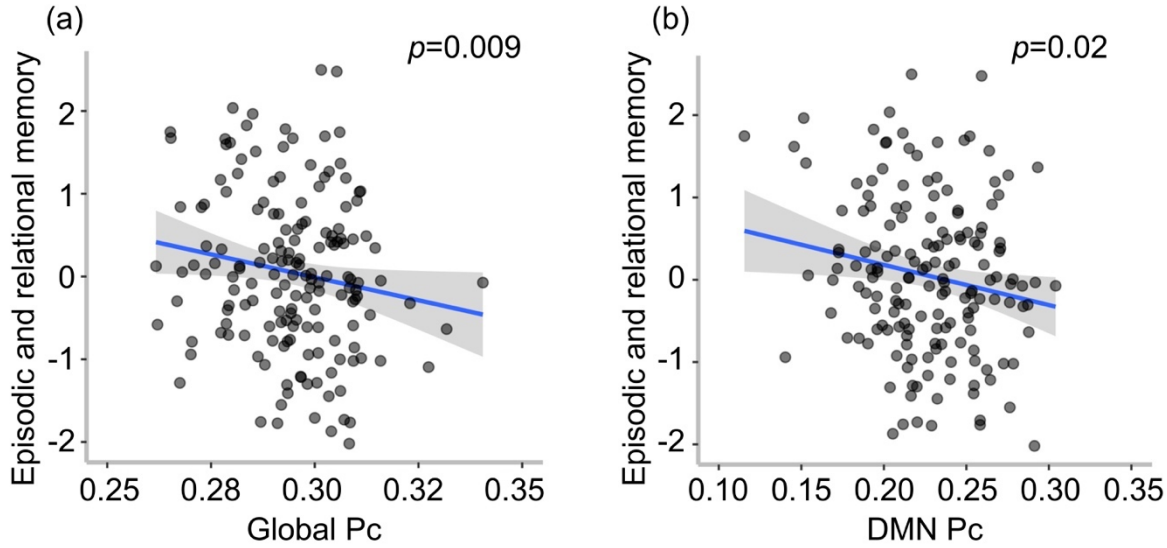

Figure 3.7 Cross-sectional associations between participation coefficient (Pc) and cognitive performance from the PREVENT-Dementia study. (a) Higher global Pc (lower network segregation) and (b) higher default mode network (DMN) Pc (lower network segregation) were significantly associated with worse episodic and relational memory at baseline.

3.4 Discussion

Functional segregation, a summary measure of brain network organisation, is an emerging measure of brain health in both normal and pathological ageing processes (Brier et al., 2014; Wig, 2017). In this study, I investigated the vulnerability of brain networks to loss of segregation during the healthy adult lifespan and in cognitively healthy midlife individuals at risk for late-onset AD, as well as the association between segregation loss and cognition in midlife. First, at the global brain level, I showed that: (i) greater network segregation was significantly associated with greater mean cortical GMV, a putative measure of brain health, consistent with previous work (Kong et al., 2020), and (ii) network segregation was

significantly reduced with increasing adult age, suggesting that brain networks become less segregated or more diffuse during healthy ageing, consistent with previous studies (Chan et al., 2014; Wig, 2017). The second relationship was further supported by a novel result from the midlife cohort of the PREVENT-Dementia study. Older age at baseline was significantly associated with reduced network segregation over two years in midlife. Taken together, these findings support that functional network segregation, in particular the participation coefficient metric, can serve as a proxy for brain health, and could be useful for detecting early changes in individuals at risk for Alzheimer's disease.

The second novel finding of this study was that females had higher network segregation than males across the adult lifespan, independent of age and educational attainment. There is currently a lack of knowledge about sex differences in network segregation. While one recent study examined the effect of sex on network segregation throughout adulthood, the results show no sex differences (Ballard et al., 2022). A possible explanation for this discrepancy could be a different metric of functional segregation used in their study compared to the current one. This new evidence suggests that it is important to consider sex differences when investigating network segregation. Therefore, the results of the present study regarding age- or AD risk-related changes were all controlled for the sex effect. Another potential implication for future research is to determine the role of sex in age- or other AD risk-related changes in network segregation (Ballard et al., 2022), which may help to explain sex differences in the prevalence and progression of Alzheimer's disease.

The investigation of network-specific age-related changes in functional segregation across the adult lifespan revealed significant changes in 5/10 networks, including three high-order networks (DMN, FPN and SN) and two sensorimotor networks (Visual and Motor 1). Previous studies addressing this research question have yielded inconsistent findings regarding which networks are susceptible to segregation loss across the adult lifespan

(Ballard et al., 2022; Cassady et al., 2019; Chan et al., 2014), possibly due to differences in statistical power associated with different sample sizes, correction methods for multiple comparisons to control for false positive rates, and measures of network segregation (Varangis et al., 2019). Despite these differences in study design, the present study, together with previous studies (Ballard et al., 2022; Chan et al., 2014; Chong et al., 2019; Grady et al., 2016; Malagurski et al., 2020; Ng et al., 2018), provides further evidence for age-related declines in functional segregation of high-order networks, supporting their vulnerability during healthy ageing.

Contradicting previous studies (Ballard et al., 2022; Cassady et al., 2020; Cassady et al., 2019; Chan et al., 2014; Manza et al., 2020), the present study found an age-related increase in functional segregation of the Motor 1 network. Although this change in direction is counterintuitive, it is consistent with some previous studies showing increased functional connectivity within the somatomotor network throughout adulthood (He et al., 2017; Mathys et al., 2014; Song et al., 2014; Tomasi & Volkow, 2012), suggesting a compensatory role of such increases in response to declining motor function. A possible reason for the discrepancy between previous studies and the current one is that there may be a non-linear relationship between age and functional segregation of the motor network across the adult lifespan (Varangis et al., 2019), leading to mixed findings when examining their linear relationship (Jockwitz & Caspers, 2021). Further studies are needed to test this hypothesis. Nevertheless, the networks that showed significant changes in functional segregation with age, particularly the high-order networks, have important implications for predicting changes in early AD processes in midlife.

Critically, the third novel finding of this study was that cross-sectionally, cognitively healthy middle-aged adults carrying an APOE ε4 allele showed greater network segregation compared to non-carriers. This change in direction is consistent with previous studies of the

same and other similar midlife cohorts showing better cognition (Gharbi-Meliani et al., 2021; Ritchie et al., 2017; Zokaei et al., 2020) (see also Chapter 2, Section 2.3), cerebral hyper-perfusion (Dounavi et al., 2021; Mak et al., 2021; McKiernan et al., 2020), and hyperconnectivity within the DMN (Cacciaglia et al., 2022; Westlye et al., 2011) in APOE ε4 carriers than in non-carriers. Importantly, greater network segregation, particularly in the DMN, was significantly associated with better episodic and relational memory cross-sectionally in this midlife cohort. The DMN has been widely recognized for its critical role in episodic memory (Dickerson & Sperling, 2009), and this novel finding from the present study further suggests that maintaining functional segregation of the DMN is crucial for better episodic and relational memory in midlife. However, the longitudinal analysis did not show a significant association between change in network segregation and change in cognition over two years, which may be due to the relatively young age range of the sample, leading to small variations in brain function and cognition changes over such a short follow-up period at the whole group level.

Furthermore, I also found that, of the ten networks (Power et al., 2011), only the DMN showed such an effect of APOE genotype. The DMN has been shown to be vulnerable to AD pathology, and its functional connectivity is disrupted at different stages of AD (Greicius et al., 2004; Habib et al., 2017; Koch et al., 2012; Kucikova et al., 2021; Sorg et al., 2007). In preclinical AD, Aβ deposition strongly overlaps with DMN regions (Buckner et al., 2005; Palmqvist et al., 2017) and is inversely associated with DMN functional connectivity in cognitively healthy older adults (Mormino et al., 2011; Palmqvist et al., 2017; Sheline, Raichle, et al., 2010). DMN functional connectivity has also been found to be disrupted in patients with MCI (Gili et al., 2011) and AD (Gour et al., 2014; Grieder et al., 2018), and to track disease progression and conversion from MCI to AD (Brier et al., 2012; Damoiseaux et al., 2012; Petrella et al., 2011). These findings highlight the vulnerability of DMN

functional connectivity across the AD spectrum. The novel findings from the current work further suggest that the DMN is vulnerable to changes in the functional organisation in middle-aged individuals who are currently cognitively healthy but at genetic risk for late-onset AD.

Another novel finding of this study was that APOE ε4 carriers, but not non-carriers, showed a significant loss of network segregation in the DMN over two years. To the best of my knowledge, this is the first study to show a prominent decline in functional segregation of the DMN with ageing in cognitively healthy middle-aged individuals at risk for late-onset AD. A greater loss of network segregation with ageing, particularly in high-order brain networks (i.e., DMN, FPN and SN), was previously shown in cognitively unimpaired older APOE ε4 carriers compared to non-carriers (Ng et al., 2018). Furthermore, reduced network segregation has also been documented in patients with AD (Dai et al., 2019; Ewers et al., 2021) and was further predictive of dementia severity (Chan et al., 2021). This novel finding from the present study extends previous findings by demonstrating an accelerated decline in functional segregation in individuals at higher risk of late-onset AD in midlife, decades before the onset of clinical manifestations of dementia.

Taken together, the present study demonstrates the impact of the largest genetic risk for sporadic AD in the Caucasian population on functional brain network organization in midlife. Further, it uncovers a previously unknown trajectory: stronger functional segregation of APOE ε4 carriers cross-sectionally, followed by a pronounced age-related loss of segregation longitudinally, relative to non-carriers. These results lend some support to a recent proposal on the impact of APOE ε4 on AD biomarker progression trajectories (Koelewijn et al., 2019), which hypothesizes a dichotomised effect of APOE ε4 on functional brain biomarkers, i.e., hyper-expression, e.g., hyperactivity / hyperconnectivity in brain regions/networks vulnerable to AD, in late young adulthood (i.e., from the 30s

onwards), and hypo-expression, e.g., hypoconnectivity in later life. In support of this hypothesis, Koelewijn et al. (2019) found significantly higher functional connectivity of brain networks as measured with MEG, particularly in the DMN, in young APOE ε4 carriers (age: 24.5 ± 5.4 years) compared to age-matched non-carriers (Koelewijn et al., 2019), but significantly reduced functional connectivity in clinical AD patients (age: 67-89 years) compared to age-matched healthy controls (Koelewijn et al., 2017). They also directly compared the effects in younger APOE ε4 carriers with older AD patients and found significant overlap in changes of specific brain areas/networks, with different directionality of change. Therefore, they speculated that the earlier hyperconnectivity of those vulnerable networks would eventually lead to their hypoconnectivity (Koelewijn et al., 2019). However, their comparisons were cross-sectional, making it impossible to draw conclusions about the longitudinal course of changes. In addition, the participants included in their study did not cover the midlife stage (Koelewijn et al., 2017; Koelewijn et al., 2019). Findings from the current study on longitudinal changes, with a specific focus on midlife, therefore, significantly advance this field. Why does the APOE genotype show a dichotomised expression in brain function across the lifespan? One possible explanation is the antagonistic pleiotropy hypothesis of aging (Williams, 1957), which proposes that deleterious genes, such as the APOE ε4 gene allele, have survived through evolution because they may confer an advantage, early in life when humans are reproductively fit.

In conclusion, this study provides evidence for selective vulnerabilities of brain networks to disruptions in network organization during healthy ageing and in cognitively healthy midlife individuals at risk for late-life AD. In particular, three high-order networks (i.e., the DMN, FPN, and SN) and two sensorimotor networks (i.e., the Visual and Motor 1 networks) were vulnerable to the age effect across the healthy adult lifespan. Of these networks, the DMN was particularly vulnerable to AD risk in midlife. The APOE ε4 genotype was significantly

associated with altered functional brain network organization in cognitively healthy individuals in midlife, an estimated 23 years from symptoms onset. Higher network segregation cross-sectionally was accompanied by loss of segregation longitudinally only in APOE ε4 carriers. These novel findings suggest that functional network segregation constitutes a novel and early substrate for the impact of genetic AD risk on the brain in midlife and thus could have implications for the early detection and intervention in AD.

Methodological considerations

The resting state fMRI data from the PREVENT-Dementia research programme presents inadequate brain coverage and inconsistent scanning angles that prevent whole brain parcellation for network analyses. To address this limitation, I adapted a comprehensive brain map (Power et al., 2011) based on individual-specific brain coverage and constructed an individualised brain network for each participant, that maximises the number of participants for the network analyses. I also replicated the findings using a different brain atlas (Raichle, 2011) that contains a smaller number of brain nodes. This ensures the same constructed brain network for each participant. In addition, I also tested the main findings using two different thresholds for participant inclusion (for details, please see Appendix B). The results were robust to these different analyses.

4. Chapter 4: Lifestyle activities contribute to cognitive reserve in cognitively healthy middle-aged individuals at risk for dementia

4.1 Introduction

In Chapters 2 and Chapter 3, I have shown that well-established risk factors for late-life Alzheimer's disease, including risk that incorporates lifestyle factors (i.e., the CAIDE score), have a significant impact on cognition and brain health in middle-aged individuals who are currently cognitively healthy. The aim of this empirical study of my thesis is to investigate whether protective lifestyle factors can mitigate the effects of AD risk on early brain and cognitive changes in midlife.

As a multidimensional construct, lifestyle has a multipronged impact on cognition and the brain. In contrast to lifestyle risks, such as the cardiovascular factors captured by the CAIDE score, several lifestyle factors have been found to protect brain health and cognition in later life. Factors such as education, activities that stimulate the brain (e.g., socialising, reading, learning new skills, regular exercise, etc.), and occupational attainment have been associated with the preservation of cognitive function in older adults (D. Chan et al., 2018) and reduced symptom severity in Alzheimer's disease (Dekhtyar et al., 2019; Livingston et al., 2020; Livingston et al., 2017; Wang et al., 2017), a phenomenon known as "cognitive reserve". These factors are thought to explain why there is considerable variability in the degree of cognitive impairment in late-onset AD (Bennett et al., 2003; Ewers et al., 2013), even when controlling for key pathologies such as beta-amyloid (Aβ) and pathological tau (Franzmeier et al., 2020; Jack & Holtzman, 2013). Therefore, the building of cognitive reserve may

contribute to the attenuation of cognitive decline and the delay in the onset of dementia, and thus may have important implications for the prevention of dementia.

One prominent account of the biological mechanisms mediating the relationship between stimulating lifestyle activities and cognitive reserve in AD (Robertson, 2013, 2014) suggests that environmental enrichment upregulates the noradrenergic system which originates in the locus coeruleus, that is otherwise depleted with age (Liu et al., 2020) and AD pathology (Jacobs et al., 2021), leading to compensatory brain mechanisms for cognitive functions.

While education and occupational attainment have been previously recognised as key drivers of cognitive reserve (Richards & Deary, 2005), there is a renewed interest in the additional contribution of other activities, that can actively be modified in midlife, such as stimulating avocational activities. Using the Lifetime of Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007), Gow et al. (2017) and D. Chan et al. (2018) found that physically, socially and intellectually stimulating lifestyle activities undertaken in midlife, independent of education, contribute to the maintenance of cognitive performance in later life, after adjusting for childhood cognitive ability (Gow et al., 2017) and early life education and midlife occupational attainment (D. Chan et al., 2018).

A rigorous definition of cognitive reserve predicts not only that lifestyle factors will be associated with better cognition, but also that such factors will moderate the relationship between brain health and cognition (Brayne et al., 2010; Song et al., 2022; Stern et al., 2020). Individuals with greater reserve are expected to be better able to cope with brain ageing or AD pathology and maintain normal cognitive function (Stern et al., 2020). In other words, the cognitive abilities of individuals with high reserve should be de-coupled from their brain status on typical measures, such as grey matter volume (Nilsson & Lövdén, 2018; Stern, 2017), and rather be realized through compensatory mechanisms. In support of this aspect

of cognitive reserve, D. Chan et al. (2018) found that physically, socially and cognitively stimulating lifestyle activities undertaken in midlife significantly moderated the relationship between total grey matter volume (GMV) and fluid intelligence in healthy older adults (aged 66-88 years). Older people with high engagement in midlife stimulating activities did not show an association between cognition and total GMV (i.e., maintained their cognitive abilities regardless of decrements in their brain structure) in contrast to those with low engagement, who showed a significant association between better cognition and higher GMV, in keeping with expectations. While this and other studies have established that stimulating activities contribute to cognitive reserve in later life and relative to established AD pathology, it remains poorly understood whether cognitive reserve can offset the effects of AD risk in midlife, while individuals are cognitively healthy. Answering this question is crucial for identifying early interventions that target modifiable factors to prevent Alzheimer's disease prior to the onset of clinical symptoms.

The present study aimed to investigate the contribution of lifestyle activities, other than education, to cognitive reserve in midlife. Specifically, I asked three research questions: (i) whether lifestyle activities interact with risk factors for late-life AD (APOE ε4 genotype, FHD and CAIDE) in affecting cognitive performance; (ii) whether lifestyle activities moderate the relationship between cognition and measures of brain health; and (iii) whether the moderation effects are present in individuals at higher risk of developing late-onset dementia. In this study, I considered two measures of brain health, i.e., total GMV for brain structural health, and functional network segregation for brain functional health (Ewers et al., 2021; Wig, 2017). For a thorough review of the evidence of functional segregation as an emerging measure of brain health, please see Chapter 3, Section 3.1.

These relationships were investigated in the same cohort discussed in previous chapters, of cognitively healthy middle-aged individuals, assessed at baseline and two years follow-up.

In order to relate the current findings to those of previous studies, I used the LEQ (Valenzuela & Sachdev, 2007), the same instrument as in the aforementioned studies (D. Chan et al., 2018; Gow et al., 2017), to evaluate stimulating lifestyle activities specific to midlife, yielding two composite factors, (a) occupation and managerial responsibility, and (b) physical, social and intellectual activities. I expected that there would be significant associations between midlife lifestyle factors and cognition in domains already shown in this cohort to be affected by risk of late-life AD (see Chapter 2, Section 2.3.3), and that midlife lifestyle factors would significantly moderate the relationship between brain health and cognition, in such a way that cognition of individuals with more engagement in these lifestyle activities would be less dependent on brain health, in line with the rigorous definition of cognitive reserve.

4.2 Methods

4.2.1 Participants

The same midlife cohort investigated in the previous chapters was included in this study (baseline N = 210; 2-year follow-up N = 188). For a detailed description of the cohort, please refer to Chapter 2, Section 2.2.1. In this chapter, I conducted three main analyses using different subsets of participants, as follows:

(i) *Subset 1: Lifestyle × risk interaction on cognition.* The same subset of participants that were used to investigate the effect of AD risk on cognition in Chapter 2 was also used to investigate the interaction between lifestyle and AD risk on cognition in this study (baseline N = 206; follow-up N = 174). Details of the inclusion/exclusion of participants can be found in Chapter 2, Section 2.2.1.

(ii) *Subset 2: Lifestyle × brain structural health interaction on cognition*. At baseline, 17 participants were excluded due to no participation or contraindications to MRI, 6 due to incidental findings on MRI scans, and 1 due to missing cognition data. At follow-up, 18 participants were excluded due to no participation or contraindications to MRI, 3 due to incidental findings on MRI scans, and 11 due to missing cognition data, resulting in N=186 at baseline and N = 156 at follow-up, for the analysis of lifestyle moderation of the association between total grey matter volume and cognition (Figure 8.1 in Appendix C).

(iii) *Subset 3: Lifestyle × brain functional health interaction on cognition*. At baseline, 17 participants were excluded due to no participation or contraindications to MRI, 6 due to incidental findings, 20 due to incomplete brain coverage for functional brain network analysis (the subset selection based on inclusion criteria has been described in detail in Chapter 3, Section 3.2.1), and 1 due to missing cognition data. At follow-up, 19 participants were excluded due to decline or contraindications to MRI, 3 due to incidental findings, and 1 due to inadequate brain coverage, and 11 due to missing cognition data, resulting in N = 166 at baseline and N = 154 at follow-up (Figure 8.1 in Appendix C)

4.2.2 Assessments

See Chapter 2 for full descriptions of the assessments used in this study, including the three risk factors (APOE ε4 allele, FHD, and the CAIDE score) in Section 2.2.2 and three cognitive domains: (i) episodic and relational memory, (ii) working and short-term (single-feature) memory, and (iii) verbal, visuospatial functions, and short-term (conjunctive) memory in Section 2.2.3, Section 2.2.4, and Section 2.3.2.

4.2.3 Measurement of lifestyle activities

The Lifetime of Experiences Questionnaire (LEQ) (Valenzuela & Sachdev, 2007), designed to take a lifespan approach to the measurement of cognitive reserve (Stern, 2009, 2012; Stern et al., 2019) and mental activity, measures engagement in a broad range of lifestyle activities across three stages of life: young adulthood (13-29 years), midlife (30-64 years) and late-life (65 years onwards). Therefore, the LEQ is preferable for looking at a midlife cohort compared to other scales that capture dementia-specific risk related to modifiable lifestyle factors (e.g., LIBRA, Schiepers et al. (2018)). The LEQ comprises sub-scores capturing "specific" activities, reflecting the primary activity undertaken in each life stage, and "non-specific" activities, reflecting engagement in physical, social and intellectual activities in any stage. For the purpose of this paper, I define midlife 'lifestyle' as all the activities captured by the LEQ (below).

Midlife specific score

The midlife specific component score centres on occupation and comprises two sub-scores that measure (a) the occupational history and (b) the managerial responsibility. For the first occupational sub-score, participants were asked to record their primary occupation in each 5-year interval from age 30 to age at assessment. Each reported occupation was scored on a scale of 0-9, according to the International Standard Classification of Occupations (ISCO 08) guidelines (https://www.ilo.org/public/english/bureau/stat/isco/isco08/). This scale relates to the skill level associated with occupations, where managers score 1, professionals 2, technicians and associate professionals score 3, and so on. Participant scores were inverted and summed. The second sub-score is a measure of the managerial responsibility associated with reported occupations. If participants indicated that they were employed in a managerial capacity, the number of people that they oversaw in four of their reported occupations was

documented. Managerial responsibility was scored as follows; 0 people = 8, 1-5 people = 16, 5-10 people = 24 and 10+ people = 32. The highest score is recorded as the managerial responsibility sub-score. The occupational history and managerial sub-scores were summed and multiplied by a normalization factor of 0.25. Normalization ensures that the midlife specific and non-specific scores have comparable mean values (Valenzuela & Sachdev, 2007).

Midlife non-specific score

The non-specific score assesses frequency of engagement in 7 activities, capturing those of a physically, socially and intellectually stimulating nature, scored on a 6-point Likert scale of frequency (never, less than monthly, monthly, fortnightly, weekly, daily). Scores range from 0 – 35, with higher scores reflecting more frequent engagement in such activities. The items included in the scale are socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engagement in physical activity that is mildly, moderately, or vigorously energetic, reading, practicing a second language, and travelling. The travel item asks participants if they have visited any of a list of continents between the ages of 30-54. Responses were scored on a 6-point scale as follows: none, 1-2 regions, 3-4 regions, 5 regions, 6 regions, 7 regions.

4.2.4 MRI acquisition and processing

Functional data acquisition and processing

Details on acquisition parameters and pre-processing of resting-state MRI data are described in Chapter 2, Section 2.2.5, and Chapter 3, Section 3.2.3. A full description of the construction of the functional brain network and the calculation of the network segregation,

indexed by the participation coefficient (Pc), can be found in Chapter 3, Section 3.2.4.

Structural data acquisition and processing

T1-weighted magnetization prepared rapid gradient echo (MPRAGE) (repetition time = 2.3 s, echo time = 2.98 ms, 160 slices, flip angle = 9°, voxel size = 1 mm^3 isotropic) scans were acquired. In an independent study by the PREVENT research team (Dounavi et al., 2022), all scans were corrected for field inhomogeneities using the Advanced Normalisation Toolbox (ANTs) N4 algorithm (Tustison et al., 2010). Freesurfer version 7.1.0 was used for data processing (Desikan et al., 2006). The recon-all pipeline was run with default settings for each participant. After recon-all, the brain masks and surfaces were inspected, and manual corrections were applied (a) in the form of erosion of non-brain voxels from the brain mask or non-WM voxels from the WM mask, (b) in the form of filling of areas where the brain was not correctly identified, or (c) with the addition of control points in cases where white matter was not successfully identified. Finally, the total GMV was derived for each participant at baseline and follow-up.

4.2.5 Statistical analyses

Due to the lack of longitudinal changes over two years in the three investigated cognitive domains (for details, see Chapter 2, Section 2.3), I considered the baseline and follow-up data separately. Over the 2-year follow-up window, a proportion of the participants in this study may have changes in brain health that are yet subthreshold to clinical manifestations. Therefore, the follow-up dataset has the potential to reveal the impact of age on the variables of interest. A p-value < 0.025, i.e., 0.05 divided by the 2 study time points, was considered

statistically significant to correct for multiple comparisons.

I used the R software for all statistical analyses. The normality of the data was assessed by combining the visualization of a quantile-quantile plot and the Shapiro–Wilk test. Demographic and clinical information of the study cohort was analysed across risk groups using chi-square (χ^2 tests) for categorical (discrete) variables and Mann Whitney U tests for continuous variables, given that they were not normally distributed in this cohort.

Subsequently, I used hierarchical regression models to look at the contribution of midlife lifestyle factors (LEQ specific and non-specific scores), risk factors (APOE ε4 genotype and FHD), and of their interactions to cognitive performance, at baseline and follow-up. The effect of APOE ε4 and CAIDE risk factors was modelled independently, in order to avoid modelling the variance associated with APOE genotype in the same model twice. In each case, dependent variables were the three cognitive domains, each assessed in a separate model.

I then assessed the moderation effects of midlife lifestyle factors on the relationship between each measure of brain health and cognition using multiple linear regression models, at baseline and follow-up. Each of the three cognitive scores was treated as a dependent variable in separate models, and midlife lifestyle factors, measures of brain health (total GMV and global functional network segregation measured by Pc, each assessed in separate models), and their interactions were treated as independent variables. Finally, post-hoc subgroup analyses were carried out according to the risk factors defined in this study to test whether these relationships were present in at-risk individuals. Specifically, I evaluated the moderation models for different risk groups.

To avoid multicollinearity, I mean-centred continuous variables (specific and non-specific scores, and CAIDE score when treated as a continuous variable). Age, sex and years of

education were included as covariates in all models except those including the CAIDE score, as these demographic variables are considered in the CAIDE. Total intracranial volume was included as an additional covariate for the models assessing the relationship between total grey matter volume and cognition.

A significant interaction effect between a risk factor and a lifestyle factor on cognition would indicate that the association between the lifestyle factor and cognitive performance differs across levels/values of the risk factor. Similarly, a significant interaction between a lifestyle factor and a measure of brain health would indicate that the brain-cognition coupling differs according to the levels of engagement in lifestyle activities in midlife. For any observed interactions, I plotted the regression of the lifestyle factor on cognition for each level/value of the risk factor, or the regression of the brain measure on cognition for each level of lifestyle factors divided by the median value (Aiken & West, 1991), to interpret the effect. I then tested the significance of the slopes of the simple regression lines, i.e., the simple slope analyses. Scatter plots showing these relationships were generated using unadjusted values, and full statistical details are provided in each legend for reference.

The variance of some parts of physical activity is accounted for twice in the model, in the CAIDE score and in the non-specific LEQ factor, resulting in a weakening of its statistical contribution that can by captured by the lifestyle factor. Therefore, any effect of physical activity that can be captured by the lifestyle factor (independent variable) in the same model CAIDE, can only provide a conservative estimate of the contribution of physical activity to the dependent variable of cognitive performance.

4.3 Results

4.3.1 Demographic characteristics

Demographic characteristics of the full cohort, stratified by APOE ε4 genotype and family history of dementia, can be found in Chapter 2, Section 2.3.1. Further specifications of the lifestyle activities are shown in Table 4.1. There were no significant differences in either the specific or non-specific LEQ scores between the risk groups at either time point (Table 4.1).

Table 4.1 Scores on the Lifetime of Experiences Questionnaire (LEQ) of the full cohort at baseline and follow-up, stratified by family history of dementia and on APOE genotype

	Baseline (n=210)			Follow-up (n=188)		
	FHD- (n=107)	FHD+ (n=103)	*p* (Mann-Whitney U)	FHD- (n=89)	FHD+ (n=99)	*p* (Mann-Whitney U)
LEQ specific score	13.8 ± 4.4	14.0 ± 6.9	0.94	14.5 ± 5.5	14.3 ± 6.0	0.75
LEQ non-specific score	18.0 ± 4.5	18.0 ± 3.0	0.28	19.0 ± 4.0	18.0 ± 4.0	0.11
	APOE ε4- (n=133)	APOE ε4+ (n=75)	*p* (Mann-Whitney U)	APOE ε4- (n=118)	APOE ε4+ (n=68)	*p* (Mann-Whitney U)
LEQ specific score	13.8 ± 6.8	14.0 ± 5.0	0.89	14.3 ± 6.6	14.4 ± 4.5	0.79
LEQ non-specific score	18.0 ± 3.0	18.0 ± 5.0	0.50	19.0 ± 4.0	19.0 ± 5.0	0.29

Note: median ± interquartile range (IQR) was reported. Abbreviations: FHD+/-, family history of dementia positive/negative; APOE ε4 +/-, Apolipoprotein ε4 genotype positive/negative.

4.3.2 Interaction of risk and protective lifestyle factors on cognition

Episodic and Relational Memory

At baseline, a hierarchical regression model with lifestyle factors, i.e., the specific and non-specific LEQ scores, risk factors (APOE ε4 and FHD), and age, sex, and years of education as covariates, and episodic and relational memory as the dependent variable (Table 8.1a in Appendix C) showed a significant positive association between episodic and relational memory and education [β (SE) = 0.09 (0.02), $p < 0.0001$] (Figure 4.1a). Similarly, this relationship was also present at follow-up [β (SE) = 0.10 (0.02), $p < 0.0001$] (Figure 4.1b). Higher education values were significantly associated with better performance at both timepoints. The inclusion of risk by lifestyle interaction terms (FHD × specific score, FHD × non-specific score, APOE ε4 × specific score, APOE ε4 × non-specific score) into the hierarchical regression model did not show any significant associations between lifestyle × risk interaction terms and cognitive performance, at baseline or follow-up (Table 8.1b in Appendix C). Education was significantly associated with cognitive performance. I, therefore, controlled for its effect throughout analyses, as I am interested in additional contributions to cognition from other lifestyle activities undertaken in midlife.

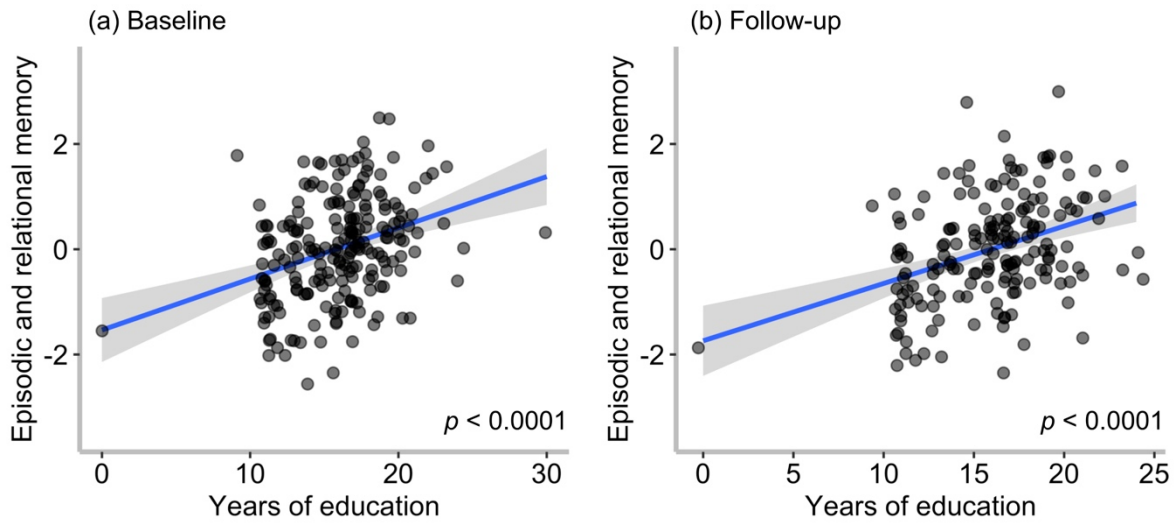

Figure 4.1 Association of years of education with episodic and relational memory performance at baseline (a) and follow-up (b). The x-axis displays the total reported years of education attained. On the y-axis, higher scores represent better episodic and relational memory performance. Scatter plots show unadjusted values. Full regression statistic for education: [β (SE) = 0.09 (0.02), p < 0.0001], at baseline; [β (SE) = 0.10 (0.02), p < 0.0001] at follow-up.

The hierarchical regression models with lifestyle factors and CAIDE as independent variables, and episodic and relational memory as the dependent variable (Table 4.2) showed a significant positive association between the non-specific LEQ factor and episodic and relational memory at both baseline [β (SE) = 0.04 (0.02), p = 0.02] (Figure 4.2a) and follow up [β (SE) = 0.07 (0.02), p = 0.002] (Figure 4.2b). More frequent engagement in physically, socially and intellectually stimulating activities was associated with better episodic and relational memory. This association was independent of CAIDE and, therefore, of age, sex, and years of education, as included in this score. The inclusion of CAIDE by lifestyle

interaction terms (CAIDE × specific score, CAIDE × non-specific score) into the hierarchical regression model did not show any significant associations between lifestyle × risk interaction terms and cognitive performance, at baseline or follow-up (Table 8.1c in Appendix C).

Table 4.2 CAIDE – Regression coefficient for Episodic and Relational Memory at Baseline & Follow-up

		Baseline			Follow-up		
Model summary		R^2	$F_{(3, 202)}$	p	R^2	$F_{(3, 166)}$	p
		0.04	3.11	0.03	0.06	3.52	0.02
DV	IV	β (SE)		p	β (SE)		p
Episodic and Relational Memory	CAIDE	-0.05 (0.03)		0.10	-0.01 (0.03)		0.78
	Specific	-0.01 (0.02)		0.64	-0.02 (0.02)		0.36
	Non-Specific	0.04 (0.02)		0.02	0.07 (0.02)		0.002

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CAIDE, Cardiovascular risk factors, Ageing and the Incidence of Dementia.

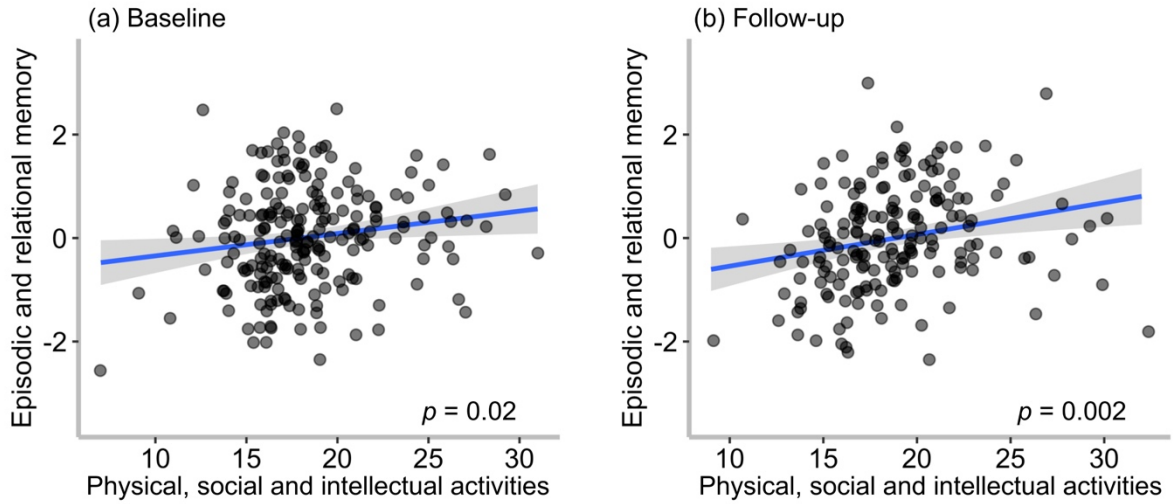

Figure 4.2 Association of physical, social and intellectual activities with episodic and relational memory performance at baseline (a) and follow-up (b). On the x-axis, higher scores represent more frequent engagement in physical, social and intellectual lifestyle activities, and on the y-axis, higher scores represent better episodic and relational memory performance. Scatter plots show unadjusted values. Full regression statistic for physical, social and intellectual activities, after controlling for education, sex, and age: [β (SE) = 0.04 (0.02), p = 0.02], at baseline; [β (SE) = 0.07 (0.02), p = 0.002] at follow-up.

Working and Short-Term (Single-Feature) Memory

No significant associations of any of the lifestyle factors or lifestyle × risk interactions with performance on the working and short-term (single-feature) memory at baseline or follow-up (Table 8.2a-d in Appendix C).

Verbal, Visuospatial Functions, and Short-Term (Conjunctive) Memory

I found no significant associations of any of the risk or lifestyle factors with performance on

verbal, visuospatial functions, and short-term (conjunctive) memory at baseline or follow-up (Table 8.3a in Appendix C). The inclusion of risk by lifestyle interaction terms in the hierarchical model revealed a significant association between the non-specific LEQ score × FHD interaction term and cognitive performance [β (SE) = 0.11 (0.05), p = 0.01] (Table 4.3) at follow-up. To interpret this interaction, I investigated the relationship between cognitive performance and the non-specific LEQ score for the FHD+ and FHD- groups independently (Figure 4.3). In particular, there was a significant positive relationship between non-specific lifestyle activities and cognition in the FHD+ group [β (SE) = 0.08 (0.03), p = 0.02], which was independent of age, sex, or years of education. I did not observe such a relationship in the FHD- group [β (SE) = -0.03 (0.03), p = 0.34]. These results suggested that for individuals with positive family history, more frequent engagement in the non-specific LEQ factor — namely physically, socially and intellectually engaging activities — was associated with better performance in verbal, visuospatial functions, and short-term (conjunctive) memory. Finally, I also observed trend associations between cognitive performance and the specific LEQ factor score × FHD interaction term [β (SE) = -0.07 (0.04), p = 0.06] at follow-up. This association, while suggestive of a role for occupational complexity on cognition, stratified by family history risk group, is weak and needs to be investigated further in future studies. Additionally, as previously reported (see Chapter 2, Section 2.3.3), higher CAIDE was associated with poorer performance on verbal, visuospatial functions, and short-term (conjunctive) memory (Table 8.3b in Appendix C). There were no significant associations of any of the lifestyle factors or interactions of CAIDE × lifestyle with cognition at either time point (Table 8.3c in Appendix C).

Table 4.3 FHD & APOE- Regression coefficient values for Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory at Baseline & Follow-up, including interaction terms

Model summary		Baseline			Follow-up		
		R^2	$F_{(11, 194)}$	p	R^2	$F_{(11, 162)}$	p
		0.09	1.76	0.06	0.09	1.48	0.14
DV	IV	β (SE)		p	β (SE)		p
Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory	Specific	0.01 (0.03)		0.75	0.01 (0.03)		0.63
	Non-specific	0.05 (0.03)		0.07	0.0004 (0.03)		0.99
	FHD	-0.22 (0.14)		0.12	0.20 (0.16)		0.20
	APOE ε4	-0.08 (0.15)		0.61	-0.19 (0.16)		0.24
	FHD * Specific	0.004 (0.03)		0.90	-0.07 (0.04)		0.06
	APOE ε4 * Specific	-0.03 (0.04)		0.36	0.06 (0.04)		0.09
	FHD * Non-specific	-0.06 (0.04)		0.19	0.11 (0.05)		0.01
	APOE ε4 * Non-specific	0.01 (0.04)		0.91	-0.07 (0.05)		0.10
	Age	-0.04 (0.02)		0.006	-0.02 (0.02)		0.19
	Sex	0.24 (0.16)		0.14	0.18 (0.17)		0.29
	Years of education	-0.02 (0.02)		0.48	0.003 (0.02)		0.89

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; APOE ε4, Apolipoprotein ε4; FHD, family history of dementia.

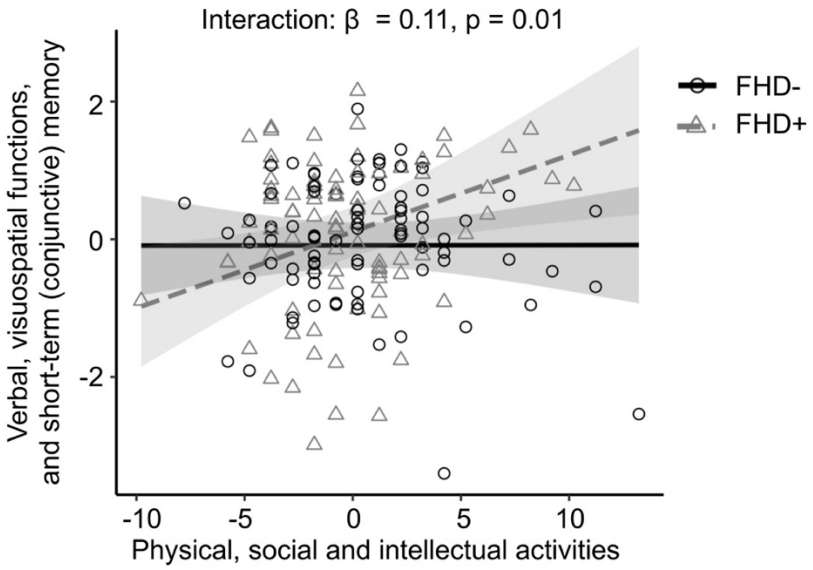

Figure 4.3 Interaction of physical, social and intellectual activities and family history of dementia on verbal, visuospatial functions, and short-term (conjunctive) memory at follow-up. On the x-axis, higher scores represent more frequent engagement in physical, social and intellectual lifestyle activities, and on the y-axis, higher scores represent better verbal, visuospatial functions, and short-term (conjunctive) memory. Physical, social and intellectual activities are mean-centred. The positive family history of dementia group showed a significant positive association between engagement in these activities and improved verbal, visuospatial functions, and short-term (conjunctive) memory. No significant association was seen for the negative family history group. The scatter plot shows unadjusted values, but the statistical significance was based on the regression analyses where I controlled for covariates. Abbreviations: FHD+, family history positive; FHD-, family history negative.

In summary, in the first part of the analysis, I found that greater engagement in stimulating lifestyle activities of a physical, social, and intellectual nature was significantly associated with better cognitive performance in midlife, independent of education. More importantly,

the benefit of midlife lifestyle was pronounced in individuals at higher risk of developing late-onset Alzheimer's disease through FHD. This suggests that these stimulating lifestyle activities mitigate the impact of AD risk on cognition early in life. In the following section, I report the results of the moderation effect of lifestyle activities on the relationship between brain health and cognition.

4.3.3 Lifestyle factors, brain structural health, and cognition

The multiple regression model with cognition as the dependent variable, lifestyle factors, total grey matter volume (TGMV), and their interaction terms (TGMV × LEQ specific score, TGMV × LEQ non-specific score) as independent variables showed no significant associations of any of the independent variables with performance on episodic and relational memory (Table 8.4 in Appendix C), or working and short-term (single-feature) memory (Table 8.5 in Appendix C), or verbal, visuospatial functions, and short-term (conjunctive) memory (Table 8.6 in Appendix C), at either baseline or follow-up, after controlling for age, sex, years of education, and total intracranial volume.

4.3.4 Lifestyle factors, brain functional health, and cognition

Episodic and Relational Memory

The multiple linear regression model with episodic and relational memory as the dependent variable, lifestyle factors, global participation coefficient (Pc), and their interactions (global Pc × LEQ specific score, global Pc × LEQ non-specific score) as independent variables, and with age, sex, and years of education as covariates showed no significant associations between the global Pc × lifestyle interaction terms and cognition at either time point (Table

8.7 in Appendix C).

Working and Short-Term (Single-Feature) Memory

There were significant associations between the global Pc × LEQ non-specific score interaction and performance on working and short-term (single-feature) memory at both baseline [β (SE) = 3.45 (1.54), p = 0.03] and follow-up [β (SE) = 2.91 (1.41), p = 0.04] (Table 8.8 in Appendix C). However, these results did not survive correction for multiple comparisons across the two study sessions.

Verbal, Visuospatial functions, and Short-Term (Conjunctive) Memory

At baseline, no significant associations were observed between verbal, visuospatial functions, and short-term (conjunctive) memory and the global Pc × lifestyle interaction terms (Table 4.4). At follow-up, there was a significant interaction between global Pc and non-specific LEQ on cognitive performance [β (SE) = 3.47 (1.40), p = 0.01] (Table 4.4). To interpret this interaction, I divided participants into low and high activity groups based on the median of the LEQ non-specific scores and examined the brain-cognition coupling for each group (Figure 4.4b). I found a significant negative relationship between global Pc and cognition for the low activity group [β (SE) = -25.89 (8.68), p = 0.003], but no relationship for the high activity group [β (SE) = 5.87 (8.18), p = 0.47]. For those with less engagement in physically, socially and intellectually stimulating activities in midlife, better cognitive performance was significantly associated with greater functional network segregation (lower global Pc), as expected. By contrast, cognition was independent of global Pc for those with greater engagement in lifestyle activities. In addition, I also found a trend association of

cognition with the global Pc × specific LEQ interaction [β (SE) = -2.92 (1.50), p = 0.05]. While this association suggests a role for occupational attainment in cognitive reserve, it is weak and needs to be further explored in future studies.

Table 4.4 Brain functional health – Regression coefficients for Verbal, Visuospatial functions, and Short-Term (conjunctive) Memory at Baseline & Follow-up

Model summary		Baseline			Follow-up		
		R^2	$F_{(8, 157)}$	*p*	R^2	$F_{(8, 145)}$	*p*
		0.07	1.40	0.20	0.09	1.73	0.10
DV	IV	β	SE	*p*	β	SE	*p*
Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory	Specific	0.02	0.02	0.36	0.006	0.02	0.76
	Non-specific	0.02	0.02	0.31	0.007	0.02	0.77
	Global Pc	-3.64	5.68	0.52	-14.00	6.27	0.03
	Global Pc * Specific	0.48	1.13	0.67	-2.92	1.50	0.05
	Global Pc * Non-specific	-0.40	1.67	0.81	3.47	1.40	0.01
	Age	-0.04	0.02	0.005	-0.02	0.02	0.30
	Sex	0.22	0.17	0.20	0.24	0.18	0.19
	Years of education	-0.02	0.02	0.54	-0.002	0.03	0.94

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; Pc, participation coefficient.

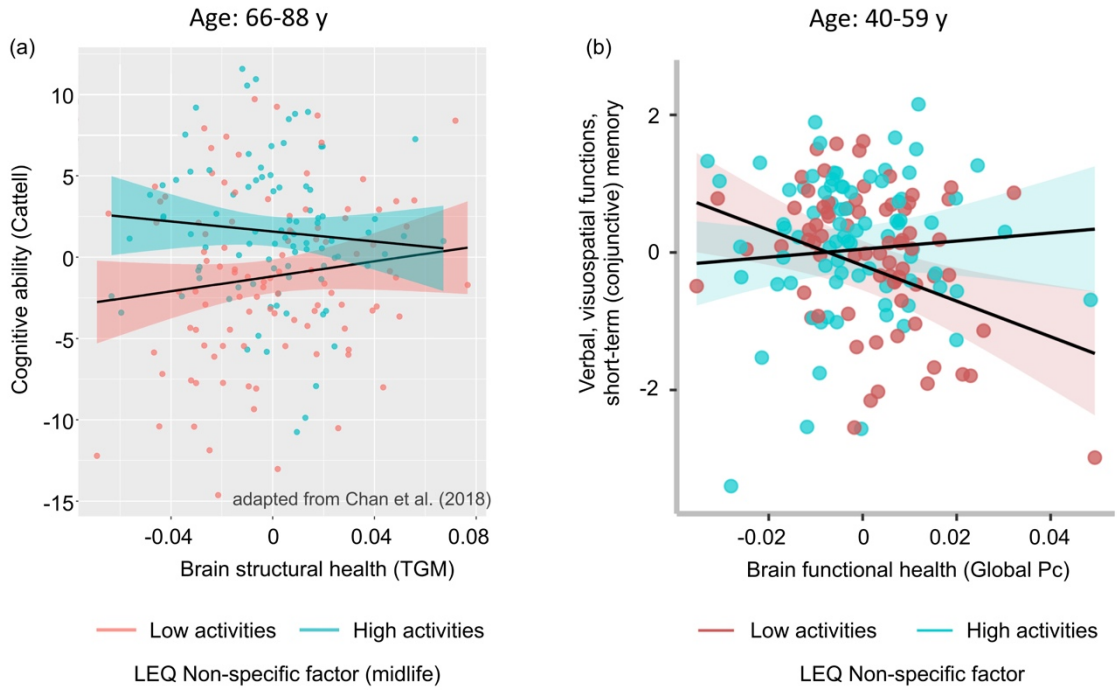

Figure 4.4 Interaction of physical, social and intellectual activities (LEQ non-specific factor) and brain health on cognition. (a) In heathy older adults (aged 66-88 years), cognitive ability of individuals with more engagement in LEQ non-specific factor at midlife was less dependent on their total grey matter volume (TGM), a common index of brain structural health (figure adapted from Chan et al., 2018). (b) In cognitively healthy middle-aged adults (aged 40-59 years), a similar interaction between the LEQ non-specific factor and a measure of brain functional health, global participation coefficient (Pc), on verbal, visuospatial functions, and short-term (conjunctive) memory was shown at follow-up. On the x-axis, higher scores represent less network segregation (poorer brain health), and on the y-axis, higher scores represent better verbal, visuospatial functions, and short-term (conjunctive) memory. Global Pc is mean-centred. Individuals with low engagement (in salmon) in LEQ non-specific factor showed a significant relationship between better cognition and greater functional brain health. No significant association was seen for individuals with greater engagement in these activities (in cyan). The scatter plot shows unadjusted values, but the statistical significance was based on the regression analyses where I controlled for covariates. Abbreviation: LEQ, Lifetime of Experiences Questionnaire. Non-specific factor assesses the frequency of engagement in 7 activities, capturing those of a physically, socially and intellectually stimulating nature, scored on a 6-point Likert scale of frequency (never, less than monthly, monthly, fortnightly, weekly, daily).

Figure 4.4b shows that I replicated the effect shown by D. Chan et al. (2018) (also presented in Figure 4.4a), on cognitive reserve, with the difference that the cohort here is middle-aged (aged 40-59 years) rather than older adults (aged 66-88 years), and that stimulating midlife activities modulate the relationship between cognition and brain functional health, rather than brain structural health as in D. Chan et al. (2018).

So far, I have shown that the cognition of individuals with more engagement in physically, socially and intellectually stimulating activities was independent of their functional brain network segregation, in keeping with the rigorous definition of cognitive reserve. Notably, the cognitive domain that showed such an effect, i.e., verbal, visuospatial functions, and short-term (conjunctive) memory, was also found to be associated with the CAIDE score (see Chapter 2, Section 2.3.3). Therefore, I carried out a post-hoc analysis to see whether such a moderation effect of lifestyle was present in people with a high or low CAIDE score at follow-up. In particular, the median split of the CAIDE was used to divide participants into the high (> 6) and low (≤ 6) risk groups.

For the high CAIDE group, there was a significant global Pc × non-specific LEQ interaction for cognition [β (SE) = 4.28 (1.83), p = 0.02] (Table 4.5). Simple slope analyses showed that higher global Pc (lower network segregation) was significantly associated with poorer cognition for individuals with low engagement in stimulating lifestyle activities [β (SE) = -33.49 (11.61), p = 0.005], but not for those with high engagement [β (SE) = -3.16 (13.22), p = 0.81] (Figure 4.5). This pattern of association was consistent with my expectation and suggests that the contribution of stimulating lifestyle activities, captured by the non-specific LEQ factor (i.e., physically, socially and intellectually stimulating activities), to cognitive reserve was present in individuals at high risk of late-life dementia as defined by the CAIDE score (CAIDE > 6). For the low CAIDE group, there was also a significant global Pc × non-specific LEQ interaction on cognitive performance [β (SE) = 5.25 (2.65), p = 0.04]. However,

simple slope analyses showed no significant associations between global Pc and cognition for either individuals with high engagement in stimulating activities or those low engagement. This result, although indicating that lifestyle moderates the brain-cognition relationship in the low CAIDE group (CAIDE ≤ 6), does not support the cognitive reserve hypothesis. Further studies are needed to investigate different pathways through which midlife lifestyle affects cognition of individuals with low risk of developing AD.

Table 4.5 Brain functional health – Regression coefficients for Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory for different at-risk groups at follow-up

		High CAIDE			Low CAIDE		
Model summary		R^2	$F_{(8, 63)}$	*p*	R^2	$F_{(8, 67)}$	*p*
		0.22	2.19	0.04	0.10	0.92	0.51
DV	IV	β	SE	*p*	β	SE	*p*
Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory	Specific	0.03	0.03	0.32	-0.02	0.03	0.51
	Non-specific	-0.01	0.03	0.74	0.06	0.04	0.14
	Global Pc	-23.79	9.35	0.01	9.37	9.96	0.35
	Global Pc * Specific	-5.07	2.87	0.08	0.22	2.06	0.91
	Global Pc * Non-specific	4.28	1.83	0.02	5.52	2.65	0.04
	Age	-0.02	0.04	0.58	0.01	0.02	0.67
	Sex	0.16	0.25	0.53	0.03	0.29	0.92
	Years of education	0.006	0.04	0.88	-0.02	0.03	0.55

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; Pc, participation coefficient. CAIDE Cardiovascular risk factors, Ageing and the Incidence of Dementia.

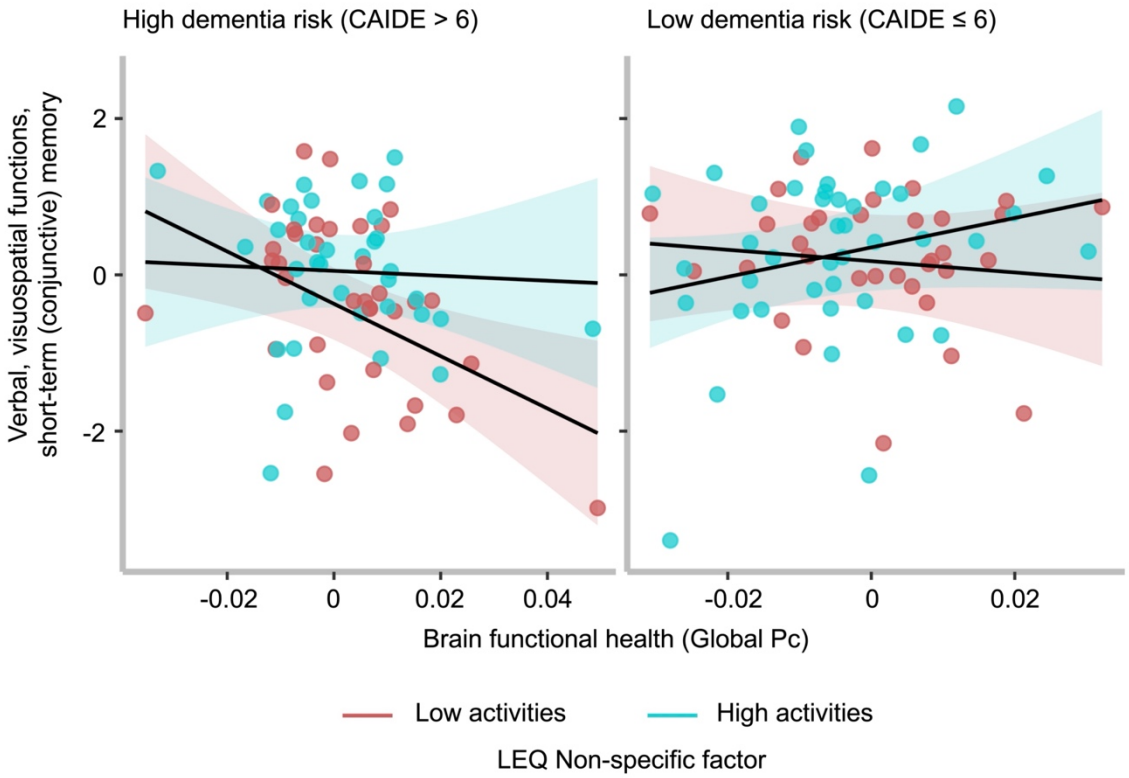

Figure 4.5 Modulation of the expected functional brain health - cognition relationship by physical, social and intellectual activities for individuals with high dementia risk at follow-up. On the x-axis, higher scores represent lower network segregation, and on the y-axis, higher scores represent better verbal, visuospatial functions, and short-term (conjunctive) memory. Global Pc is mean-centred. The expected moderation effect was present for individuals with high Cardiovascular risk factors, Ageing and the Incidence of Dementia (CAIDE) risk score (> median=6), but not for those with low CAIDE (≤ 6). Specifically, simple slope analyses showed a significant association between better cognition and greater functional brain network segregation only for individuals with low engagement (in red), but not for those with high engagement in these lifestyle activities (in blue). The scatter plot shows unadjusted values, but the statistical significance was based on the regression analyses where I controlled for covariates. Abbreviation: LEQ, Lifetime of Experiences Questionnaire. Non-specific factor assesses the frequency of engagement in 7 activities, capturing those of a physically, socially and intellectually stimulating nature, scored on a 6-point Likert scale of frequency (never, less than monthly, monthly, fortnightly, weekly, daily).

4.4 Discussion

It is now acknowledged that Alzheimer's Disease processes are present decades before the onset of clinical symptoms (Jack et al., 2010; Ritchie et al., 2015), but whether lifestyle factors can already protect against these early AD processes in middle-aged individuals who are cognitive unimpaired but at risk for late-life AD remains poorly understood. In this study, I asked whether stimulating lifestyle activities contribute to cognitive reserve in midlife and, if so, whether cognitive reserve can offset AD risk at such an early stage. I did this in two ways. First, I investigated the relationship between stimulating lifestyle activities and cognition in middle-aged individuals, who are cognitively healthy but at risk for late-life AD. Second, I tested the hypothesis that a decoupling of cognition from typical measures of brain health could be observed in middle-aged adults with high engagement in stimulating lifestyle activities, especially in individuals at higher risk of developing future dementia. Lifestyle activities significantly impacted cognition in midlife. Individuals with greater educational attainment showed stronger cognition in a composite dimension capturing episodic and relational memory. This result is consistent with a previous study (Ritchie et al., 2017) of this cohort showing that visuospatial abilities were positively associated with education. It is also consistent with epidemiological studies on older adults showing that education contributes to cognitive reserve in older life (Richards & Deary, 2005). The studied cohort is highly educated, with approximately 30% reaching a post-graduate qualification study (Ritchie et al., 2017). As the education measure captures the total years of education, the observed effect of education reflects long-term effects set in motion from early life and young adulthood.

The key question in this study, however, was to investigate any additional contribution of activities undertaken in midlife, independent of education. The first novel finding of this study was that more frequent engagement in physically, socially and intellectually

stimulating activities in midlife was associated with stronger cognition in episodic and relational memory, both at baseline and at follow-up. This effect was independent of sex, age, years of education, and cardiovascular factors captured by the CAIDE score as well as occupational attainment. The second novel finding was that physically, socially and intellectually stimulating activities undertaken in midlife had a significant effect on the cognition of middle-aged individuals at risk for late-life AD. Specifically, higher engagement in these activities was associated with significantly stronger cognition in another composite dimension, capturing verbal, visuospatial functions, and short-term (conjunctive) memory in cognitively healthy individuals, who were at risk for late-life AD through a family history of dementia, at follow-up. Importantly, this effect was independent of age, sex, and years of education. The presence of this effect in the follow-up but not the baseline dataset is likely due to the older age of the cohort at follow-up. Short-term (conjunctive) memory functions have been found to be impaired in the pre-symptomatic stages of AD (Parra et al., 2010). Additionally, impaired visuospatial function is one of the earliest cognitive deficits observed in AD (Laukka et al., 2012; Williams et al., 2020) and has previously been linked to increased AD risk in this cohort (Ritchie et al., 2017) (see also Chapter 2, Section 2.3.3). In similarly cognitively healthy, but older (> 65 years) North American cohorts (Miron et al., 2019; Noble et al., 2010), changes in cerebrospinal fluid biomarkers related to inflammation have been associated with changes in visuospatial cognitive performance, thereby suggesting a biochemically-mediated effect of early pathology in presymptomatic individuals.

Taken together, these results suggest that stimulating lifestyle activities may boost cognitive functions that are very vulnerable to AD risk and early AD neuropathology (Laukka et al., 2012; Parra et al., 2010; Williams et al., 2020). Physically, socially and intellectually stimulating midlife activities have been shown to influence late-life cognition (D. Chan et

al., 2018; Gow et al., 2017), suggesting that they contribute to the cognitive reserve that mitigates the effect of age-related cognitive decline and AD neuropathology. Findings from the current study advance understanding by showing that engagement with these activities contributes to cognitive reserve to risk of AD, or even incipient AD neuropathology, from midlife, in individuals who are presently cognitively healthy.

Family history of dementia is a well-established risk factor (Berti et al., 2011; Donix et al., 2012; Scarabino et al., 2016), independent of the genetic risk bestowed by the APOE ε4 genotype, that captures both genetic and environmental risk influences. For example, an individual who has one or more parents with dementia, may, independently to the presence of the APOE ε4 genotype, be exposed to negative environmental influences that contribute to neuropathology, including increased stress (Franks et al., 2021), caregiver burden (Chiao et al., 2015; Yu et al., 2015) and reduced participation in enriching environments due to caregiving duties (Ross & Carroll, 2017). Therefore, alongside contributing to cognitive reserve, enhanced engagement with physically, socially and intellectually stimulating activities may positively impact individuals with a family history of dementia by counteracting these negative environmental influences.

The third novel finding was that physically, socially and intellectually stimulating activities undertaken in midlife significantly moderate the relationship between functional brain network segregation and cognition in verbal, visuospatial functions, and short-term (conjunctive) memory at follow-up. As predicted, only individuals with low engagement in these activities show a positive relationship between functional network segregation and cognition. By contrast, individuals with high engagement do not show this relationship, suggesting that they realize cognition via independent compensatory brain mechanisms bolstered by cognitive reserve (D. Chan et al., 2018). These effects were independent of education, occupational attainment, age, and sex. This finding replicates the moderation

effect of midlife lifestyle activities on the brain-cognition relationship shown by D. Chan et al. (2018) in healthy older adults (aged 66-88 years). Not only do I show this relationship for the first time in middle-aged adults (40-59 years), but also I show that the relevant brain health measure that appears to be affected by stimulating lifestyle activities in this age group is functional network segregation, which is increasingly recognised as a marker of brain functional health and has previously been found to be associated with better cognitive function, such as long-term memory, across the healthy adult lifespan (Chan et al., 2014; Wig, 2017).

In contrast to previous findings (D. Chan et al., 2018), I did not find a significant moderation effect by lifestyle activities on the relationship between the typical structural measure of brain health (i.e., total grey matter volume) and cognition. This null effect is likely due to the relatively young age of this cohort, on average 23 years before the estimated dementia onset (Dounavi et al., 2022), and it suggests that brain structure does not exhibit a significant impact of lifestyle in midlife, relative to the typically investigated older populations (D. Chan et al., 2018).

The fourth novel finding was that the expected moderation effect of lifestyle activities on brain-cognition association was seen in individuals with a high CAIDE score (CAIDE > 6), independent of education, occupational attainment, age, and sex. The CAIDE score incorporates several lifestyle risk factors (i.e., blood pressure, cholesterol, physical activity, body mass index) that reflect cardiovascular dementia risk. It has been used to select at-risk participants (CAIDE > 6) for a large randomised controlled trial (RCT), the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), to prevent cognitive impairment in older adults (age > 60 years). Another large RCT, the French Multidomain Alzheimer Preventive Trial (MAPT) in older adults (age > 70 years), found a significant beneficial effect of lifestyle interventions in individuals with a CAIDE > 6. These

observations highlight the potential intervention effects in participants with a particular risk profile. The results of the current study that the investigated stimulating lifestyle activities contribute to cognitive reserve in individuals with a high CAIDE score in midlife extend these large RCTs (please see Kivipelto et al. (2018) for a review) and suggest that engagement in those lifestyle avocational activities in midlife may attenuate or delay cognitive decline associated with Alzheimer's disease in later life.

What might be the mechanism by which stimulating activities impact cognition and brain health in midlife? Models of Alzheimer's disease delineated by neuropathological staging (Braak & Braak, 1991) place the locus coeruleus (LC), a small nucleus in the pontine tegmentum region of the brainstem, at the pathogenesis of AD from late young adulthood and early midlife (30-40 years) (Arnsten et al., 2021; Jacobs et al., 2021; Márquez & Yassa, 2019). The LC is responsible for the production of the neurotransmitter noradrenaline (NA) (Amaral & Sinnamon, 1977), a major driver of the brain's arousal system, which strongly modulates high-order cognition. Novelty provides a key trigger for arousal, and thus LC–NA activity occurs strongly in response to novel stimuli. Studies (Robertson, 2013, 2014) have suggested that environmental enrichment through lifestyle stimulating activities, such as those investigated in this study, upregulates the noradrenergic system, which is otherwise depleted with age (Liu et al., 2020) and AD pathology (Jacobs et al., 2021), leading to compensatory brain mechanisms for cognitive function, such as the strengthening of the fronto-parietal brain and other large-scale brain networks.

In summary, the findings of the current study suggest that modifiable lifestyle activities may offset AD risk-related cognitive decrements, contribute to cognitive reserve in midlife and support the targeting of certain modifiable lifestyle activities for the prevention of Alzheimer's Disease, especially in those at higher risk of developing AD through FHD or CAIDE. These activities include socializing with family or friends, practicing a musical

instrument, practicing an artistic pastime, engagement in physical activities, reading, practicing a second language, and travelling. Given the apparent lifestyle contributions both as risk and protective factors of dementia (Livingston et al., 2020), a healthy lifestyle may be the individual's current best defence against sporadic late-onset AD. The modifiability of the lifestyle activities identified here renders them promising cost-effective candidates for intervention and prevention strategies from early life. These activities may be particularly significant for non-pharmacological interventions for AD in low and middle-income countries, where barriers to education are more prevalent than in high-income countries (Livingston et al., 2020).

Methodological considerations

As education is strongly positively linked to IQ (Ritchie & Tucker-Drob, 2018) and the cohort in this study was highly educated, the question of reverse causation arises (Borgeest et al., 2020; D. Chan et al., 2018; Gow et al., 2017). This points to the possibility that cognitive abilities may determine engagement in stimulating activities, rather than the inverse. However, the effect on midlife verbal, visuospatial functions, and short-term (conjunctive) memory is independent of the total years of education, which shows that education does not directly drive this effect. Furthermore, I found that midlife lifestyle activities were associated with improved cognitive performance only in the family history positive group, which is not, at least not prima facie, more educated than the family history negative group. Thus, this effect is likely independent of any indirect effects of education.

The long-term effect of more engagement in lifestyle activities on cognition is not obtained in this study due to the lack of longitudinal change in cognition over two years. The use of composite cognitive domains that capture slightly different functions in the two assessment

points (Please see Chapter 2, Section 2.2.3, Section 2.2.4, and Section 2.3.2 for details) may reduce the power to accurately detect cognitive changes over time. Nevertheless, previous studies from this cohort have shown only subtle changes over the two-year period (Dounavi et al., 2021; Low et al., 2021), possibly due to the relatively young age range of the sample and the short follow-up window (Ritchie et al., 2018; Ritchie et al., 2017). Future studies following this cohort for a longer period of time, i.e., five years, will be undertaken to address the longitudinal impact of lifestyle activities in this cognitively healthy middle-aged cohort, particularly in those at risk of late-life Alzheimer's disease.

Finally, I caution that the interpretability of the effect of lifestyle activities on each individual function is limited by their composite assessment in this study and requires individuation in future studies with a longer longitudinal follow-up window.

5. Chapter 5: General Discussion

5.1 Summary of findings

It is now well acknowledged that AD pathophysiological processes start decades before clinical manifestations, while the indicators and brain mechanisms of sporadic AD in midlife are poorly understood. Answers to these questions will help to identify the target population in whom early prevention or intervention strategies, such as lifestyle changes, are likely to have the greatest effect to delay or prevent the onset of dementia. The present thesis aimed to address two main research questions: 1) How does brain function, cognition, and the relationship between the two change during midlife, in individuals who are presently cognitively healthy but at risk for late-onset AD? 2) Can stimulating lifestyle factors (physical, social and intellectual activities) mitigate such early changes in midlife? Below I review the thesis' main and novel findings and reflect on future research directions opened up by these findings.

5.1.1 Associations of APOE genotype with brain functional integrity and cognition

The novel finding in Chapter 2 was that the APOE ε4 allele, the main genetic risk factor for late-onset sporadic AD (Donix et al., 2012; Liu et al., 2013), was significantly associated with better performance in episodic and relational memory. The novel finding in Chapter 3 was that APOE ε4 carriers had significantly greater segregation of functional brain networks at baseline and significant loss of network segregation over two years, indicating prominent age-related decrements of functional network segregation, relative to non-carriers. These effects were independent of age, sex, and years of education.

For the first time, I reported the association between the genetic risk for late-life AD and episodic memory, the hallmark cognitive dysfunction in early clinical dementia and mild cognitive impairment (Irish et al., 2011) in cognitively healthy middle-aged individuals. This finding highlights the importance of studying the origins of Alzheimer's disease in this age group, over 20 years before typical symptom onset.

The trajectory of functional brain network segregation in APOE ε4 carriers lends some support to a recent proposal charting the progression of functional brain biomarkers for Alzheimer's disease (Koelewijn et al., 2019). Koelewijn et al. (2019) proposed a dichotomised manifestation of functional markers for AD, with hyperexpression, e.g., hyperactivity / hyperconnectivity, in late young adulthood (i.e., 30s onwards) and early midlife, and hypoexpression, e.g., hypoactivity / hypoconnectivity, in later life. In support of this hypothesis, the researchers found significantly higher functional activity and connectivity of brain networks, particularly the DMN, in young APOE ε4 carriers (age: 24.5 ± 5.4 years) compared to age-matched non-carriers (Koelewijn et al., 2019), but significantly reduced functional connectivity in clinical AD patients (age: 67-89 years) compared to age-matched healthy controls (Koelewijn et al., 2017). However, their comparisons were cross-sectional, making it difficult to draw conclusions about the course of changes. In addition, the participants included in their study did not cover the midlife stage (Koelewijn et al., 2017; Koelewijn et al., 2019). Findings from the current thesis on longitudinal changes, with a specific focus on midlife, therefore, complement their findings in supporting this hypothesis.

Why is this major genetic risk factor associated with a dichotomised manifestation of functional markers across the lifespan? Koelewijn et al. (2019) speculated that carrying the APOE ε4 allele may lead to early neuronal hyperactivity/hyperconnectivity, either directly by altering the excitation/inhibition balance (Nuriel et al., 2017) or through association with amyloid deposition (Stargardt et al., 2015). By directly comparing the effects in young

APOE ε4 carriers with older AD patients who showed hypoconnectivity (Koelewijn et al., 2017) between brain regions that partially overlap with the hyperconnected regions seen in young APOE ε4 carriers, they speculate that the early abnormality/hyperconnectivity will lead to eventual disconnections later in life as the disease progresses (Koelewijn et al., 2019). Alternatively, the pattern of hyperexpression in early life and hypoexpression in late life in APOE ε4 carriers is consistent with the concept of antagonistic pleiotropy from evolutionary biology (Williams, 1957), which proposes that deleterious genes, such as the APOE ε4 gene allele, have survived through evolution because they may confer an advantage early in life when humans are reproductively fit (Han & Bondi, 2008; Tuminello & Han, 2011). This is supported by my finding of better performance in episodic and relational memory in APOE ε4 carriers compared to non-carriers in midlife (see Chapter 2) and by previous studies in younger cohorts showing that younger APOE ε4 carriers cognitively outperform non-carriers (Alexander et al., 2007; Wright et al., 2003; Yu et al., 2000). The superior performance of young/middle-aged APOE ε4 carriers may also underlie a compensatory response that supports more efficient cognitive performance in the presence of incipient AD-related pathology (Cacciaglia et al., 2022). Nevertheless, the novel findings from the present work advance the current understanding of early changes in brain functional networks and cognition in cognitively healthy middle-aged individuals at genetic risk for late-onset Alzheimer's disease.

5.1.2 Associations of CAIDE with brain function and cognition

In contrast to the effect of the APOE ε4 genotype, a higher CAIDE dementia risk score was significantly associated with worse cognition in a composite domain comprising verbal, visuospatial functions, and short-term (conjunctive) memory cross-sectionally at both study

timepoints (see Chapter 2). Visuospatial and navigational abilities have previously been found to be vulnerable to CAIDE risk in the same midlife cohort as the current one (Ritchie et al., 2018; Ritchie et al., 2017). However, the novel finding in Chapter 2 was that CAIDE significantly moderated the relationship between the functional connectivity of two brain regions vulnerable to early AD pathology – the locus coeruleus (LC) and the hippocampus – and cognitive performance in the same composite domain capturing verbal, visuospatial functions, and short-term (conjunctive) memory at follow-up. In particular, higher LC–Hippocampus functional connectivity was associated with better cognitive performance for individuals with low CAIDE scores, and with worse cognitive performance in those with high scores.

The CAIDE score captures several cardiovascular risk factors, i.e., systolic blood pressure, cholesterol, physical activity, and body mass index, as well as age, sex, education, and the genetic risk factor APOE ε4 genotype. Importantly, performance in this cognitive domain, comprising verbal, visuospatial functions, and short-term (conjunctive) memory, was not significantly associated with the APOE ε4 genotype, sex, or education at either timepoint. Furthermore, the effect of CAIDE on cognition or brain-cognition association was maintained when age was additionally controlled for in the statistical models. Therefore, the observed effects are likely to be driven primarily by midlife cardiovascular risk factors included in this dementia risk score.

What might be the underlying physiological processes that drive the opposite direction of the association between higher LC–Hippocampus connectivity and cognitive performance? On the one hand, the LC is the main brain site of noradrenaline production (Amaral & Sinnamon, 1977) and, thus, the originating node of the brain's arousal system (Aston-Jones & Cohen, 2005; Sara, 2009). The LC sends noradrenergic projections to most of the brain and therefore plays a key role in cognitive processes (Sara, 2009). Animal studies have

demonstrated that the co-release of noradrenaline and dopamine from the LC terminals in the hippocampus is critical for successful spatial learning and memory (James et al., 2021; Kaufman et al., 2020; Kempadoo et al., 2016). Human studies in healthy older adults are consistent with these data and show that higher LC–Hippocampus functional connectivity is significantly associated with better memory (Jacobs et al., 2015). The findings from the current thesis complement these previous studies and suggest that the higher connectivity between the LC and the hippocampus supports verbal, visuospatial functions, and short-term (conjunctive) memory in middle-aged individuals who have better cardiovascular health.

By contrast, in middle-aged individuals with higher CAIDE scores, higher LC–Hippocampus functional connectivity was associated with worse cognitive performance. This association may be explained by the vulnerability of the LC to AD pathology, i.e., pTau accumulation in the early stages of the disease. The LC is the earliest site of tau pathology deposition (Braak & Del Tredici, 2015), which correlates with progressive grey matter loss (La Joie et al., 2019) and cognitive impairment (Giannakopoulos et al., 2003). Given the essential modulatory role of the LC in cognition, early AD pathology in the LC plays a key role in determining cognitive abilities due to incipient AD in preclinical populations (Betts, Kirilina, et al., 2019; Mather & Harley, 2016). In particular, some of the vascular risk factors included in the CAIDE score, such as cholesterol and systolic blood pressure, have been directly associated with an increased level of tau accumulation in cognitively normal older adults who harboured AD pathology (age: 68.3 ± 8.5 years) (Bos et al., 2019) and in patients with subjective or mild cognitive impairment (age: 60.8 ± 8.5 years) (Enache et al., 2016), thereby likely enhancing neurodegeneration in preclinical or prodromal stages of Alzheimer's disease.

In addition, previous studies in older adults have shown that these midlife cardiovascular risk factors are associated with an increased risk of dementia (Gottesman, Albert, et al.,

2017), brain atrophy (Swan et al., 1998) and cognitive decline (Gottesman et al., 2014; Launer et al., 1995; Rawlings et al., 2014). Furthermore, studies in the same midlife cohort from the PREVENT-Dementia research programme have shown that higher CAIDE is significantly associated with the progression of cerebral small vessel disease and systemic inflammation (Low et al., 2022), which, in turn, are increasingly associated with neurodegeneration, as well as with macrostructural brain alterations (Dounavi et al., 2022) and greater rates of brain volume loss (O'Brien et al., 2020). Taken together, these findings suggest that cardiovascular risk, as captured by the CAIDE score, is associated with impaired brain health from midlife.

In keeping with this, observational studies have shown that a CAIDE score of more than 12 confers a probability of 16.4% for future dementia, with a score of more than 8 associated with a probability of more than 4% (Kivipelto et al., 2006). In a study of individuals with a mean age of 46 years, participants with a score greater than 8 had a 29% 40-year risk of dementia (Exalto et al., 2014). These findings suggest that a proportion of the participants in the current study with a CAIDE score greater than 8 will develop dementia. Assuming that tau pathology is underway in a proportion of individuals with high dementia risk scores, the result from the present study lends indirect support to the hypothesis that LC hyperactivity and associated hyperconnectivity initiates the spread of pathological tau to the MTL, particularly the hippocampus, in the early stages of AD (Weinshenker, 2018). The ensuing neurodegeneration may explain why hyperconnectivity is associated with worse cognition in individuals with high CAIDE scores. These novel results advance the current understanding of early alterations in brain–behaviour relationships due to incipient AD in preclinical populations.

Contrary to my expectations, there was no significant change in LC–Hippocampus functional connectivity in relation to AD risk at midlife. One possible reason could be that

functional changes between the LC and MTL regions, which may reflect tau seeding and propagation from the LC (Braak & Braak, 1991; Ehrenberg et al., 2017; Gilvesy et al., 2022), have not yet reached the threshold for statistical significance at such an early stage. In patients with mild cognitive impairment (age: 65.1 ± 4.5 years), functional connectivity of the LC with the hippocampus/parahippocampus was found to be significantly reduced compared to age-matched healthy controls (Jacobs et al., 2015). A recent study of asymptomatic middle-aged adults, offspring of late-onset AD patients, found significantly reduced connectivity of the LC with the cerebellar cortex, but not the MTL regions, compared to those without a family history (Del Cerro et al., 2020). The authors speculated that neuropathological mechanisms other than the propagation of tau pathology might mediate the impaired connectivity of the LC to the cerebellum. Future longitudinal studies with the PREVENT full cohort (N=700) will provide opportunities to investigate alterations of LC–Hippocampus functional connectivity in relation to AD risk in midlife with greater statistical power.

Altogether, I provide early proof that the recruited cohort, with a mean age of 52/54 years at baseline/follow-up, did not, when genetic risk was considered, demonstrate alterations of brain–behaviour relationships that support the putative mechanism of tau pathology spread during incipient AD. It was only when a risk score incorporating cardiovascular risk factors was considered, that alterations were unravelled. These results shed light on the brain mechanism of incipient AD neuropathology in individuals who are at high risk for late-life dementia but presently cognitively healthy, and highlight the importance of targeting the modifiable risk factors relating to cardiovascular health in early intervention programmes.

5.1.3 Midlife stimulating lifestyle factors offset the effects of AD risk in midlife

Risk and protective lifestyle factors often co-occur throughout a person's life and interact in determining cognitive decline or dementia. In contrast to the aforementioned modifiable cardiovascular risk factors captured by the CAIDE score, accumulating evidence has shown that lifestyle factors, such as education, occupational complexity, and physically, socially and intellectually stimulating activities are associated with the preservation of cognitive function in older adults (D. Chan et al., 2018) and reduced symptom severity in AD (Dekhtyar et al., 2019; Livingston et al., 2020; Livingston et al., 2017; Wang et al., 2017), contributing to cognitive reserve. These lifestyle factors are thought to account for, in late-life AD, the substantial variability in the level of cognitive impairment (Bennett et al., 2003; Ewers et al., 2013) in the presence of key pathologies, including Aβ and pathological tau (Franzmeier et al., 2020; Jack & Holtzman, 2013). It remains an open research question, however, as to whether building up cognitive reserve in midlife can offset the risk of AD in the early stages.

In addition, while epidemiological evidence strongly suggests that education contributes to cognitive reserve in later life (Richards & Deary, 2005), this reflects the long-term effects of education set in motion in early life and young adulthood. Renewed interest in the research area has focused on the additional contribution of other activities undertaken in midlife, given their potential modifiability (D. Chan et al., 2018). In the following section, I discuss the main findings of the current thesis, i.e., the effects of stimulating lifestyle factors, other than education, on cognitive outcomes and brain-cognition associations in relation to AD risk factors in midlife.

The first novel finding in Chapter 4 was that more frequent engagement in physically, socially and intellectually stimulating activities was significantly associated with better

episodic and relational memory, independent of sex, age, years of education as captured by the CAIDE score, and occupational complexity in cognitively healthy middle-aged individuals. Previous studies have shown that greater engagement in these midlife lifestyle activities is associated with better late-life cognition, after adjusting for early-life cognitive ability (Gow et al., 2017) and education and occupational complexity (D. Chan et al., 2018). The present findings extend these previous findings by demonstrating the beneficial effects of these lifestyle activities on cognition in midlife.

The second novel finding in Chapter 4 was that greater engagement in these stimulating lifestyle activities in midlife was significantly associated with better cognitive ability comprising verbal, visuospatial functions, and short-term (conjunctive) memory in individuals with a family history of dementia. This effect was independent of age, sex, and years of education. Short-term (conjunctive) memory functions have been found to be impaired in the pre-symptomatic stages of AD (Parra et al., 2010). Additionally, impaired visuospatial function is one of the earliest cognitive deficits observed in AD (Laukka et al., 2012; Williams et al., 2020) and has previously been linked to increased AD risk in this cohort (Ritchie et al., 2018; Ritchie et al., 2017). In Chapter 2, I also found that the same composite cognitive domain, i.e., verbal, visuospatial functions, and short-term (conjunctive) memory, was declined with increasing dementia risk as measured by the CAIDE score. In similarly cognitively healthy, but older (> 65 years) North American cohorts (Miron et al., 2019; Noble et al., 2010), changes in cerebrospinal fluid biomarkers related to inflammation have been associated with changes in visuospatial cognitive performance, thereby suggesting a biochemically-mediated effect of early pathology in presymptomatic individuals. Taken together, the results from the present study suggest that stimulating lifestyle activities in midlife may boost cognitive functions that are very vulnerable to AD

risk and early AD neuropathology, particularly in individuals at higher risk of late-onset dementia through a family history of dementia.

Family history of dementia is a well-established risk factor (Berti et al., 2011; Donix et al., 2012; Scarabino et al., 2016), independent of the genetic risk bestowed by APOE ε4 genotype, that captures both genetic and environmental risk influences. For example, an individual who has one or more parents with dementia, may, independently to the presence of the APOE ε4 genotype, be exposed to negative environmental influences that contribute to neuropathology, including increased stress (Franks et al., 2021), caregiver burden (Chiao et al., 2015; Yu et al., 2015) and reduced participation in enriching environments due to caregiving duties (Ross & Carroll, 2017). Therefore, enhanced engagement with physically, socially and intellectually stimulating activities may positively impact individuals with a family history of dementia by counteracting these negative environmental influences.

The third novel finding in Chapter 4 was a significant moderation effect of these midlife stimulating activities on the relationship between functional brain network segregation, an emerging measure of functional brain health (Ewers et al., 2021; Wig, 2017), and cognitive performance in verbal, visuospatial functions, and short-term (conjunctive) memory at follow-up. This effect was independent of years of education, age, sex, and occupational attainment. The fourth novel finding in Chapter 4 was that the expected moderation effect by these midlife activities on the brain function-cognition relationship was present only in individuals at higher risk of developing AD according to the CAIDE score (CAIDE > 6). I did not find a similar pattern for individuals with a low CAIDE score. This effect was also independent of years of education, occupational attainment, age, and sex.

As discussed in detail in Chapter 3, the brain comprises intrinsically wired functional networks (Crossley et al., 2013; Smith et al., 2009). Each network consists of a set of distinct

and closely interconnected areas (Cole et al., 2014; Smith et al., 2009) that often work together for specialised cognitive and functional processing (Sporns & Betzel, 2016; Wig, 2017). Such modular functional organisation of the brain in the form of distinct networks has been shown to be critical for cognition (Achard et al., 2006; Bullmore & Sporns, 2012; Chan et al., 2014). In keeping with this, in Chapter 3, I found that higher functional network segregation was significantly associated with better episodic and relational memory in the midlife cohort from the PREVENT-Dementia research programme. Furthermore, this brain network property has been shown to be vulnerable to normal and pathological ageing. Decrements of functional network segregation have been found in healthy ageing (Chan et al., 2014; Wig, 2017) and in Alzheimer's disease (Ewers et al., 2021). In Chapter 3, I also found age-related longitudinal declines in functional segregation in midlife, particularly in APOE ε4 carriers. This is consistent with findings in cognitively unimpaired older APOE ε4 carriers (Ng et al., 2018). Taken together, these previous and current findings suggest that the functional segregation of brain networks is an important measure of brain health.

Against this background, the moderation effect by physically, socially and intellectually stimulating activities on the relationship between functional network segregation and cognition suggest that these midlife lifestyle activities contribute to cognitive reserve in midlife, in keeping with a rigorous definition of cognitive reserve (D. Chan et al., 2018; Stern et al., 2020). This finding replicates the moderation effect of midlife lifestyle activities on the brain health-cognition relationship shown by D. Chan et al. (2018) in healthy older adults (aged 66-88 years). Not only do I show this relationship for the first time in middle-aged adults (40-59 years), but I also show that the relevant brain health measure that appears to be affected by stimulating lifestyle activities in this age group is functional network segregation.

In contrast to the findings of D. Chan et al. (2018), I did not find a significant moderation effect by stimulating lifestyle activities on the relationship between the typical structural measure of brain health (i.e., total grey matter volume) and cognition. This null effect is likely due to the relatively young age of this cohort, on average 23 years before the estimated dementia onset (Dounavi et al., 2022), and it suggests that brain structure-cognition relationship does not exhibit a significant influence of lifestyle in midlife, relative to the typically investigated older populations (D. Chan et al., 2018).

The expected moderation effect of stimulating lifestyle factors on brain function-cognition relationship was only shown in individuals with a higher CAIDE score (CAIDE > 6). This is consistent with my expectations based on previous RCT studies (for a review, see Kivipelto et al. (2018)). As discussed earlier, the CAIDE captures many modifiable cardiovascular risk factors that have been shown to predict the incidence of late-onset dementia (Exalto et al., 2014; Kivipelto et al., 2006). Therefore, the FINGER trial, a large multidomain RCT, used CAIDE scores (CAIDE > 6) to select participants for a lifestyle intervention and found that lifestyle modifications could prevent cognitive impairment in older adults (age > 60 years) (Ngandu et al., 2015). In addition, the MAPT trial, another large multidomain RCT, included older adults (age > 70 years) with both low and high CAIDE scores and found a significant beneficial effect of the lifestyle intervention in participants with a high CAIDE score (CAIDE > 6) in particular (Andrieu et al., 2017). These findings suggest the potential effects of the lifestyle intervention in participants with a higher CAIDE score. The present findings contribute to this area of research (Kivipelto et al., 2018) and suggest that the stimulating lifestyle activities measured here may offset the AD risk conferred by the CAIDE score in midlife.

Another implication of these findings is that functional network segregation might serve as a marker for assessing the effectiveness of intervention or prevention strategies. Existing

evidence has shown that modifiable lifestyle factors, such as socioeconomic characteristics (M. Y. Chan et al., 2018) and educational attainment (Chan et al., 2021), are associated with greater functional network segregation, which in turn is associated with lower dementia severity (Chan et al., 2021; Ewers et al., 2021), even after accounting for established AD pathology and APOE ε4 genotype (Chan et al., 2021).

Overall, the findings of the present thesis suggest that stimulating lifestyle factors contribute to cognitive reserve in midlife, and benefit people at higher risk of future dementia more than those at lower risk. These activities include socializing with family or friends, practicing a musical instrument, practicing an artistic pastime, engaging in physical activities, reading, practicing a second language, and travelling. Given the apparent lifestyle contributions both as risk and protective factors of dementia (Kivipelto et al., 2018; Livingston et al., 2020), a healthy lifestyle may be the individual's current best defence against sporadic late-onset AD. The observation that the impact of midlife lifestyle was independent of educational attainment and occupational status also suggests that public health initiative aimed at boosting cognitive reserve via enhancement of midlife lifestyle is generalizable to the entire adult population, including individuals with limited access to education in early life and individuals with less engagement in occupational activities. The modifiability of the lifestyle activities identified here renders them promising cost-effective candidates for intervention and prevention strategies from early life. These activities may be particularly significant for non-pharmacological interventions for AD in low and middle-income countries (LMIC), where barriers to education are more prevalent than in high-income countries (Livingston et al., 2020).

5.2 Future directions

Up to this point, I have discussed the main and novel findings of this thesis, thus opening up certain future directions, including: (1) the potential mechanism underlying the positive association between lifestyle activities and cognitive ability; (2) the relative contribution of different lifestyle components to cognitive reserve; (3) the replicability and generalisability of the results of this thesis; (4) the effect of other risk factors; and (5) the longitudinal predictions of the current findings. I elaborate on each of these points in the following section.

5.2.1 Mechanism underlying the association between lifestyle activities and cognition

In this thesis, I have provided evidence supporting the idea that stimulating lifestyle activities contribute to cognitive reserve in cognitively healthy middle-aged individuals, particularly those at higher risk of developing late-life AD. This suggests that these lifestyle activities may reduce the risk of or delay the onset of cognitive impairments associated with late-life AD (Pettigrew et al., 2020; Rovio et al., 2005; Soldan et al., 2020; Tolppanen et al., 2015). However, the underlying mechanisms by which stimulating activities benefit cognition in midlife remain unclear. One potential pathway to shed light on this is to investigate the relationships between stimulating lifestyle activities and the structural integrity of the LC and its functional interactions with the MTL regions, and how these relationships are associated with cognitive outcomes. The LC is responsible for the production of the neurotransmitter noradrenaline (NA) (Amaral & Sinnamon, 1977), a major driver of the brain's arousal system, which strongly modulates higher-order cognition (Sara, 2009). Novelty, a key attribute of stimulating activities, is an important trigger for arousal, and thus LC–NA activity occurs strongly in response to novel stimuli. On the other hand, the LC is vulnerable to AD pathology, i.e., pTau deposition, in the earliest stage of Alzheimer's

disease (Braak & Del Tredici, 2015), which correlates with progressive grey matter loss (La Joie et al., 2019) and cognitive impairment (Giannakopoulos et al., 2003). Therefore, it has been hypothesised that environmental enrichment upregulates the noradrenergic system originated in the LC, which otherwise depletes in the presence of AD pathology (Jacobs et al., 2021), leading to compensatory brain mechanisms for cognitive functions, and thus protecting against early neurodegeneration due to pTau deposition.

In order to improve the ability to test this potential mechanism, a key issue that needs to be addressed is the precise localisation of the LC in the human brain in vivo. Despite numerous animal and human post-mortem studies documenting LC function and its important role in the pathogenesis of Alzheimer's disease (Chen et al., 2022; Mather & Harley, 2016; Sara, 2009), non-invasive *in vivo* assessment of the human LC is hampered by the small size of the nucleus and its location deep in the brainstem (Astafiev et al., 2010; Keren et al., 2009). With advances in various MRI techniques, *in vivo* structural and functional imaging of the LC in human studies is now an invaluable experimental tool for the analysis of noradrenergic dysfunction in neurodegenerative diseases. In Chapter 2, I used an LC mask created with reference to two published LC maps with relatively high specificity, developed using state-of-the-art MRI technology (Dahl et al., 2022; Ye et al., 2021). I demonstrated that functional connectivity of the LC with the hippocampus was differentially associated with cognitive performance in cognitively healthy middle-aged adults at different risks for late-life Alzheimer's disease. This effect was replicated using another published LC map (Tona et al., 2017), suggesting the robustness of the finding. Although directly applying published LC maps allows me to compare the LC function between different risk groups, future studies are needed to validate these findings by incorporating a higher resolution neuromelanin-sensitive imaging sequence to localise the LC more precisely at the individual level (Mäki-Marttunen & Espeseth, 2021). Improvements in LC localisation will also help to test the

hypothesis that structural and functional integrity of the LC underlies the positive association between stimulating lifestyle activities and cognitive outcomes in cognitively healthy middle-aged individuals.

In addition, as the brain site of origin for noradrenaline generation, the LC may also be key to the protective effects of lifestyle factors on the whole brain function, such as strengthening fronto-parietal and other large-scale brain networks (Robertson, 2013, 2014). Therefore, another potential avenue for elucidating the brain mechanisms by which stimulating lifestyle factors enhance cognitive functions vulnerable to AD risk or attenuate cognitive decline associated with AD is to examine whether and how stimulating lifestyle activities are associated with functional connectivity between the LC and large-scale functional brain networks, and their relationships with cognitive outcomes in midlife.

The analysis of large-scale functional brain networks requires satisfactory brain coverage of fMRI data, which is currently a technical consideration in the PREVENT research programme. The PREVENT study was originally designed with a particular focus on the functional properties of the MTL regions where NFT accumulates (Ritchie & Ritchie, 2012), resulting in inadequate brain coverage of fMRI data. This, in turn, affects the analysis of large-scale brain network connectivity or organisation. The analysis of functional network organisation conducted in the present thesis carefully considered the issue of brain coverage (for details, see Chapter 3). In specific, I have applied different brain parcellation schemes (Power et al., 2011; Raichle, 2011) to define brain networks and have shown consistent results supporting that the observed effect of the genetic risk factor, APOE ε4 genotype, on functional brain network segregation is not significantly affected by the coverage issue. Nevertheless, future studies using fMRI data with full brain coverage are needed to validate these findings. Addressing this issue would also improve the ability to investigate the potential implementation of cognitive reserve in midlife, for example, whether midlife

lifestyle contributes to cognitive reserve through compensatory brain network reorganisation (Nilsson & Lövdén, 2018; Stern, 2017).

5.2.2 The relative contribution of different lifestyle activities to cognitive reserve

An important follow-up question based on my findings supporting the cognitive reserve hypothesis is the relative contribution of the different intellectual, social and physical components of lifestyle to cognitive reserve. This question was not addressed in the present thesis because the instrument used in the current work produced a composite score of 7 activities and was not designed to separate these different components. Very little is currently known about the relative effects of different leisure activities on cognitive outcomes in midlife. The few studies that have looked at the effects of one or a few different avocational activities separately have shown mixed effects on cognition in midlife. For example, both physical and cognitive activities are associated with better cognition cross-sectionally (Mosconi et al., 2018; Neth et al., 2020), but none of them significantly predicted longitudinal changes (over three years) in cognition after accounting for baseline cognitive ability (Walters et al., 2018). This discrepancy may be due to confounding factors such as sex and age group, and these previous studies also did not compare the relative contribution of physical and cognitive activities. In addition, there is a lack of evidence on the impact of social activities. Therefore, future studies are needed that complement the LEQ with specific measures for each of these midlife activity components.

5.2.3 Replicability and generalisability

The release of the full PREVENT cohort (N=700) across the five research centres (Cambridge, Oxford, Imperial College London and Edinburgh Universities in the UK and Trinity College Dublin in Ireland) will provide an opportunity to test the replicability of the findings reported in this thesis (N=210) with greater statistical power and the generalisability of these findings in a larger cohort. For example, the cohort studied in this thesis has an over-representation of females (approximately 70% female at both time points), which limits the generalisability of the present findings. However, a more balanced sex ratio will be achieved in the full cohort dataset, which will help to facilitate the generalisability of the current findings to other populations.

5.2.4 Extended investigation on the impact of AD risk in midlife

The release of the full PREVENT cohort (N=700) will also provide an opportunity to extend the current investigation of risk factors of late-onset AD. For example, sex, as a biological variable, is also an important risk factor for AD. Two-thirds of people with AD are female, and despite this sex disparity, its impact on brain health and cognition in cognitively healthy middle-aged individuals at risk of late-life AD is not well understood. In this present thesis, I treated sex as a covariate in all analyses and controlled for its effect on the measures of interest. However, I found some interesting associations between sex and brain measures, and cognition. Future studies using the full cohort will include sex as a risk factor and clarify its role in modulating the impact of other risk and protective lifestyle factors on brain health and cognition.

With the full PREVENT-Dementia cohort (N=700), it will also be feasible to extend the current investigation of the effect of APOE ε4 genotype on functional network organization

and cognition. The APOE ε4 gene variant increases the risk of AD in a manner proportional to the number of copies inherited, i.e., gene dose-dependent effect (Corder et al., 1993; Farrer et al., 1997). Furthermore, neuroimaging studies have also shown dose-dependent effects of the APOE ε4 allele on *Aβ* deposition (Morris et al., 2010; Reiman et al., 2009), cerebral metabolism (Protas et al., 2013; Reiman et al., 2005), brain morphological properties (Cacciaglia et al., 2018; Martí-Juan et al., 2021), and white matter microstructure (Operto et al., 2019) in cognitively healthy individuals. A recent study demonstrated reduced resting state functional connectivity with increasing APOE ε4 allele load in the DMN and the MTL networks in cognitively healthy middle-aged individuals (Cacciaglia et al., 2022). These previous results indicate that the more APOE ε4 copies a person inherits, the more substantial the influences on the brain, even before symptoms arise. It is, therefore, of particular interest to test the gene dose-dependent effect of the APOE ε4 allele on functional network segregation. However, to increase statistical power, in this thesis, I binarized the group based on individuals with ≥ 1 copy of the ε4 allele to investigate its effect on brain function and cognition. Future studies with the full PREVENT dataset will have the potential to disentangle the effect of ε4 heterozygotes from that of ε4 homozygotes.

5.2.5 Long-term predictions

In this thesis, I found no significant longitudinal change in cognition over two years (see Chapter 2). This may be due to the relatively young cohort (aged 40-59 years). Given this age range, two years may be too short to manifest significant longitudinal change, as also suggested by other studies of the same cohort (Dounavi et al., 2021; Dounavi et al., 2020). Future studies with a longer follow-up window (the third wave of data collection is currently

underway with five years of follow-up) will be important for tracing the impact of AD risk on cognitive and brain trajectories from midlife onwards.

In addition, this cohort will be followed up with a longer time window, and this will provide an opportunity to test the predictive value of some of the current findings from the development of AD up to clinical diagnosis. The present work focused on healthy middle-aged individuals, estimated to be, on average, about 23 years from the onset of dementia based on the age at diagnosis of their parents (Dounavi et al., 2022). The participants at risk were stratified based on family history of dementia, APOE genotype, and the CAIDE dementia risk score. However, there is no way of knowing whether the higher-risk participants will all eventually develop Alzheimer's disease. Ongoing follow-up will be invaluable in assessing the validity of some of these measures in clinical use.

5.3 Conclusion

In conclusion, the aim of this thesis was to investigate changes in brain function and cognition and their relationships in cognitively healthy middle-aged individuals at risk of late-onset Alzheimer's disease. I further aimed to investigate whether midlife lifestyle activities can mitigate such early changes. The major genetic risk factor, APOE ε4 genotype, was associated with better cognition and brain functional network integrity at baseline, but more pronounced longitudinal declines over two years. These findings are consistent with a recently proposed functional brain marker trajectory hypothesis for Alzheimer's disease (Koelewijn et al., 2019) and support the antagonistic pleiotropy hypothesis (Williams, 1957), suggesting that functional network organisation may serve as a sensitive early marker of AD. In addition, the well-established dementia risk score, CAIDE, was significantly associated with worse cognition and significantly moderated the relationships between LC–

Hippocampus functional connectivity and cognition, independent of age, sex, education, and APOE genotype. This suggests an important role for midlife cardiovascular risk factors and highlights the importance of targeting these modifiable lifestyle factors. On the other hand, lifestyle factors, including physically, socially and cognitively stimulating activities, significantly contributed to cognitive reserve in cognitively healthy middle-aged individuals. In particular, more engagement in these activities in midlife was significantly associated with better cognition and moderated the relationship between brain function and cognition, especially in individuals at higher risk of developing late-life dementia. These findings suggest that a healthy lifestyle may reduce the risk of or delay the onset of dementia by enhancing cognitive reserve from midlife. Taken together, these findings suggest that future studies with a focus on midlife should adopt a multifactorial approach to further disentangle the effects of risk and protective factors on brain and cognitive health, which will help to deepen the current understanding of the indicators and underlying mechanisms of AD at an early stage. This may also have important clinical and policy implications for the improved design and implementation of lifestyle interventions to protect brain health in at-risk populations.

6 Appendix A – Supplementary materials in Chapter 2

6.1 Methods and Materials

6.1.1 Cognitive variables

The eleven cognitive summary variables from the COGNITO battery were:

1. Working memory: the simultaneous presentation of auditory and visual attention tasks assessed by subtracting the time taken in milliseconds on this double task from the visual task alone.
2. Working memory: the simultaneous presentation of auditory and visual attention tasks assessed by total number of correct answers for visual form recognition on this double task.
3. Narrative recall: total number of correct elements on immediate recall of a story with a temporal progression requiring attention to macrostructure.
4. Description recall: total number of correct elements recalled of a description without thematic progression requiring attention to microstructure and recall of spatial location. The narrative and description recall are similar in terms of word frequency in the language and syntactic structure.
5. Implicit memory: difference in the number of steps in the progressive build-up of names on the screen required for recognition between names never seen and number of names previously learnt in an immediate recall task.
6. Name-face association: number of faces recognized after a delay from a series of 18 faces of which 9 have been previously shown with their corresponding names.

7. Form perception: number of correct answers in the matching of complex forms to a multiple-choice array.
8. Form perception speed: mean time taken in milliseconds for each trial.
9. Phoneme comprehension: number of correct responses in the matching of a word with an image presented as part of a multiple-choice array including semantic, morphological and phonetic distractors.
10. Phoneme comprehension speed: mean time taken in milliseconds to perform.
11. Verbal fluency: total sum of the number of words generated in 30s using both a semantic (vegetables) and phonemic (letter P) cue.

The two summary variables from the Visual Short-term Memory Binding task were:

12. Visual short-term memory binding test (shape only condition): percentage of correct recognition of the shape of presented visual stimuli after a short period of retention.
13. Visual short-term memory binding test (shape-color binding condition): percentage of correct recognition of combinations of shape and color of presented visual stimuli after a short period of retention.

6.1.2 Behavioural data reduction

Sharp breaks in the “scree" plot of the successive eigenvalues suggest the appropriate number of components to extract. I also conducted a parallel analysis that compares the scree of components of the actual data with that of a random data matrix of the same size as the original (Horn, 1965). The detailed steps are: 1) I simulated a random normal data matrix of the same number of original cognitive variables (n=13) and the same number of participants (n=208 at baseline and n=166 at follow-up). 2) I extracted eigenvalues from the simulated

data matrix. I repeated these two steps 500 times to create a set of 500 parallel eigenvalues. 3) I took the mean and 95th percentile of all eigenvalues generated by principal components analysis of random data sets. The results were a vector of mean (and 95th percentile) eigenvalues equal in size to the original number of cognitive variables (n=13). 4) I compared the eigenvalues of the actual data to that of parallel random data sets. Specifically, I plotted eigenvalues from the actual and random data sets and kept only those components whose eigenvalues are greater than 95th percentile of eigenvalues from the random data sets. Figure 2.2a in Chapter 2 shows the scree plots of eigenvalues based on the actual data matrix (in blue line) and simulated data matrices at baseline (left panel) and follow-up (right panel). The mean eigenvalues are in dashed grey line, and the 95th percentile of eigenvalues are in red line. The shaded areas indicate that the eigenvalues of components based on the actual data were larger than the mean and 95th percentile of eigenvalues from the random data sets. Figure 2.2b shows the proportion of variance that each component explained, and the cumulative variance of the three components.

6.1.3 Framewise displacement calculation

Differentiating head realignment parameters across frames yields a six-dimensional timeseries that represents instantaneous head motion, which can then be summarised as a scalar quantity, framewise displacement (FD), using the formula (Equation (1)). Specifically, this measure was calculated as the sum of the absolute values of the derivatives of the six realignment parameters (Power et al., 2012). Rotational displacements were converted from degrees to millimetres by calculating the displacement on the surface of a sphere with a radius of 50 mm, which is approximately the mean distance from the cerebral cortex to the centre of the head.

$$\boldsymbol{FD_i} = |\Delta \boldsymbol{d_{ix}}| + \left|\Delta \boldsymbol{d_{iy}}\right| + |\Delta \boldsymbol{d_{iz}}| + |\Delta \boldsymbol{\alpha_i}| + |\Delta \boldsymbol{\beta_i}| + |\Delta \boldsymbol{\gamma_i}| \qquad (\mathbf{1})$$

Where $\Delta \boldsymbol{d_{ix}} = \boldsymbol{d_{(i-1)x}} - \boldsymbol{d_{ix}}$ and similarly for the other rigid body parameters $\left[\boldsymbol{d_{iy}}, \boldsymbol{d_{iz}}, \boldsymbol{\alpha_i}, \boldsymbol{\beta_i}, \boldsymbol{\gamma_i}\right]$.

6.2 Results

6.2.1 Cognitive components

The components can be interpreted by mapping out the cognitive functions that the highest loading measures tapped into (Figure 2.3a). For the first component (C1), given that the highest loading measures were assessing response accuracy, and were positively loaded on C1, higher value means better performance. The cognitive functions that the highest three loading measures tapped into were verbal (narrative recall), spatial (description recall), and relational memory (name-face association). Accordingly, C1 was labelled as 'episodic and relational memory'. For the second component (C2), the highest loading measures were assessing both response accuracy and latency. As accuracy measures were positively, and latency measures were negatively loaded on C2, higher value means better performance. Based on the cognitive functions that the highest loading measures tapped into, C2 was labelled as 'working and short-term (single-feature) memory'. For the third component (C3), the highest loading measures were also assessing both response accuracy and latency. By contrast to C2, accuracy measure was negatively, and latency measures were positively loaded on C3. Therefore, higher value means poorer performance. For clarity of graphical display and comparison to the other two, I reversed the signs of the values to make larger values represent better performance. Based on cognitive functions that the highest loading measures tapped into, C3 was labelled as 'verbal, visuospatial functions, and short-term (conjunctive) memory'.

6.2.2 Validation analyses with APOE ε2ε4 carriers excluded

The prevalence of APOE ε2ε4 in the studied cohort is 0.02% (Figure 6.2). To test whether the main findings were confounded by the inclusion of APOE ε2ε4 carriers, I also performed analyses excluding APOE ε2ε4 carriers. I found a significant positive association of the APOE ε4 allele with episodic and relational memory at baseline [β (SE) = 0.27 (0.14), p = 0.05] and at follow-up [β (SE) = 0.30 (0.15), p = 0.05], independent of sex, age and years of education. APOE ε4 carriers performed significantly better than non-carriers. No significant associations of the APOE ε4 allele with performance in the other two cognitive domains were observed. These results were consistent with the main findings where APOE ε2ε4 carriers were included (Figure 2.4) (Table 2.2).

In addition, Spearman correlation analyses showed a significant negative association of CAIDE (including APOE genotype) with verbal, visuospatial functions, and short-term (conjunctive) memory at baseline (rho = -0.16, p = 0.02) and at follow-up (rho = -0.19, p = 0.01). Higher CAIDE was significantly associated with poorer cognitive performance. No significant associations of CAIDE with the other two cognitive domains were observed. These results were also consistent with the main findings when I used CAIDE scores that included APOE ε2ε4 allele (Figure 2.5).

Additionally, there was no significant association between any of the risk factors and the LC–Hippocampal functional connectivity, either cross-sectionally or longitudinally, which is also consistent with the main findings, with APOE ε2ε4 carriers included.

Lastly, CAIDE (including APOE genotype) showed a significant moderation effect on the relationship between LC–Hippocampus functional connectivity and cognition comprising verbal, visuospatial functions, and short-term (conjunctive) memory at follow-up [β (SE) =

-0.45 (0.22), p = 0.04], consistent with the main findings when I used CAIDE scores including the APOE ε2ε4 allele (Figure 2.7) (Table 2.4).

Taken together, these results suggest that the inclusion of APOE ε2ε4 carriers did not affect the main results.

6.2.3 Correlation between baseline and follow-up LC–Hippocampus functional connectivity

I found a significant positive correlation of the LC–Hippocampal functional connectivity between the two study time points (r = 0.28, p = 0.01) (Figure 6.3).

6.3 Supplementary Figures and Legends

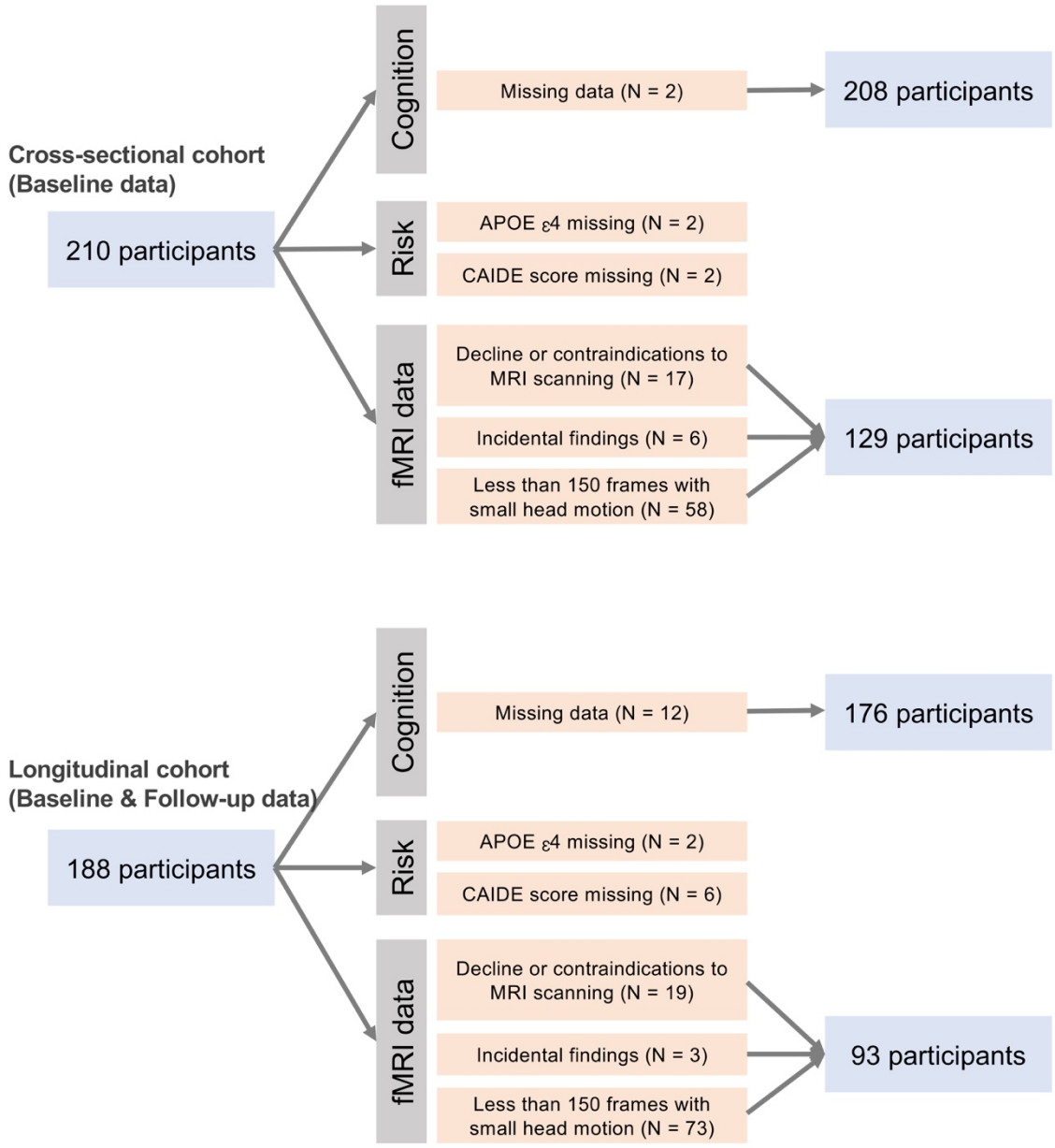

Figure 6.1 Participant inclusions for different analyses.

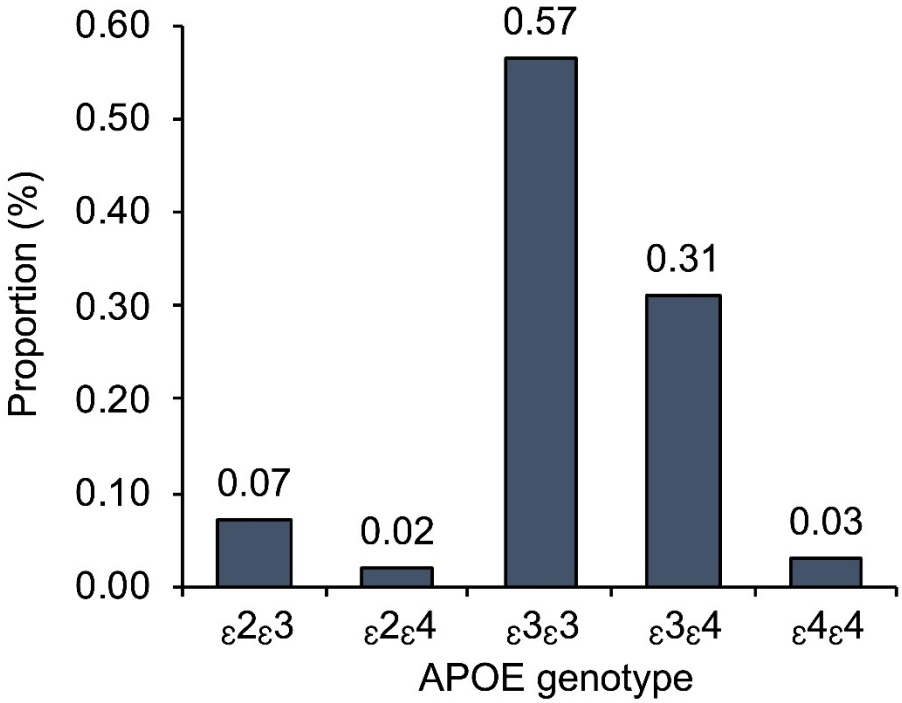

Figure 6.2 The prevalence of APOE genotype.

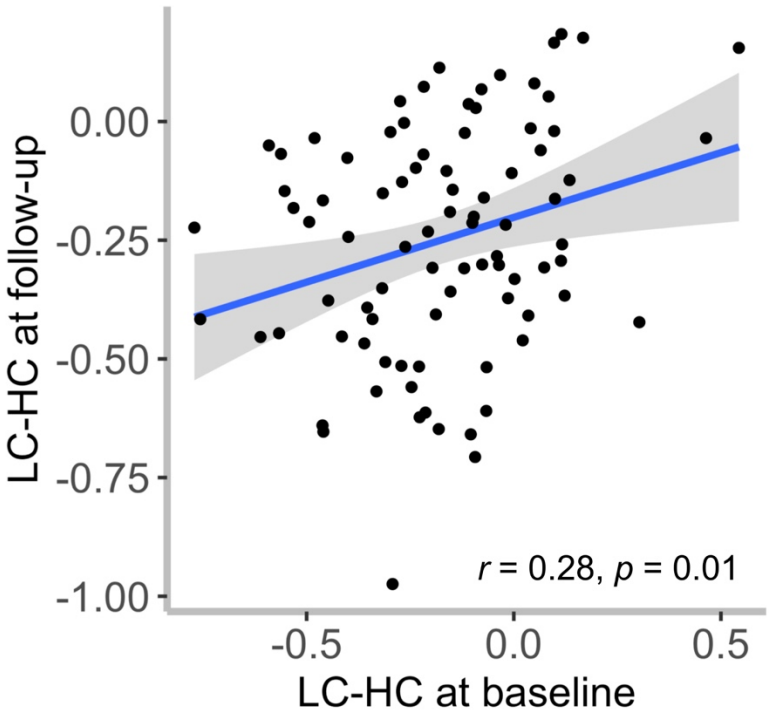

Figure 6.3 Correlation between baseline and follow-up for the locus coeruleus – hippocampus (LC-HC) functional connectivity.

6.4 Supplementary Tables

Table 6.1 Complete list of risk factors and tests obtained at baseline and follow-up

Baseline	Follow-up
Risk factors	**Risk factors**
FHD	*FHD*
APOE ε4 (Missing = 2)	*APOE* ε4 *(*Missing = 2)
*CAIDE (*Missing = 2)	*CAIDE (*Missing = 6)
Age	Age
Sex	Sex
Yeas of education	Yeas of education
Systolic blood pressure	Systolic blood pressure
BMI	BMI (Missing = 1)
Cholesterol	Cholesterol (Missing = 2)
Physical activity	Physical activity (Missing = 1)
APOE ε4 (Missing = 2)	*APOE* ε4 (Missing = 2)
Neuropsychological assessments	**Neuropsychological assessments**
COGNITIO	*COGNITIO* (Missing = 4)
Working memory	Working memory
Narrative recall	Narrative recall
Description recall	Description recall
Implicit memory	Implicit memory
Name-face association	Name-face association
Form perception	Form perception
Phoneme comprehension	Phoneme comprehension
Verbal fluency	Verbal fluency
VSTMBT (Missing = 2)	*VSTMBT* (Missing = 8)
Neuroimaging data	**Neuroimaging data**
fMRI (Missing = 17)	*fMRI* (Missing = 19)

Abbreviations: FHD, family history of dementia; *APOE* ε4, Apolipoprotein ε4; CAIDE, Cardiovascular Risk Factors, Aging and Incidence of Dementia; BMI, body mass index; VSTMBT, visual short-term memory binding test; fMRI, functional magnetic resonance imaging.

Table 6.2 Description of cognitive tasks and measures

Cognitive Tasks	Measures	Task Description	Descriptive Statistics (N=210, baseline)	Descriptive Statistics (N=188, follow-up)
Working memory	Total number of correct answers	Dual task: The subject must locate the targeted shapes and count the sounds.	Mean = 9.75 SD = 0.54 Range = 3.00 Missingness = 0	Mean = 9.85 SD = 0.51 Range = 3.00 Missingness = 4
	Mean time (ms) difference in milliseconds between the dual task and a simple form recognition task	Dual task: The subject must locate the targeted shapes and count the sounds. Simple task: Subject must locate the targeted shapes only.	Mean = 223.09 SD = 3175.07 Range = 18238.00 Missingness = 0	Mean = -55.47 SD = 2919.28 Range = 17750.00 Missingness = 4
Narrative recall	Total number of correct answers	The subject must recall a series of elements which have a logical sequence (a short story).	Mean = 13.25 SD = 4.73 Range = 23.00 Missingness = 0	Mean = 15.03 SD = 4.30 Range = 23.00 Missingness = 4
Description recall	Total number of correct answers	The subject must recall a series of elements which have a visual sequence (a short description).	Mean = 12.63 SD = 4.34 Range = 20.00 Missingness = 0	Mean = 13.39 SD = 4.73 Range = 25.00 Missingness = 4
Implicit memory	Difference the number of names never seen and the number of names already learned	The subject must recognize as soon as possible a name which is constructed progressively on the screen.	Mean = 1.05 SD = 0.83 Range = 8.20 Missingness = 0	Mean = 1.11 SD = 0.69 Range = 5.00 Missingness = 4

Name-face association	The number of correctly recognized faces and their corresponding names	The subject must decide whether a face on the screen appeared before and if yes, what the person's name is.	Mean = 5.37 SD = 2.21 Range = 9.00 Missingness = 0	Mean = 5.86 SD = 2.02 Range = 9.00 Missingness = 4
Form matching	Total number of correct answers	The subject must discriminate form and line orientation by matching a sample complex figure to one of six figures. Distractor figures are designed to detect visuospatial field neglect and difficulties with line orientation.	Mean = 6.45 SD = 1.12 Range = 7.00 Missingness = 0	Mean = 6.43 SD = 1.01 Range = 4.00 Missingness = 4
	Mean time (ms) for correct answers		Mean = 5841.64 SD = 1425.88 Range = 7596.00 Missingness = 0	Mean = 6071.80 SD = 1567.05 Range = 8116.00 Missingness = 4
Phoneme comprehension	Total number of correct answers	The subject must choose an object illustrating a presented word among 6 objects which include shape, phonetic and semantic distractors.	Mean = 8.62 SD = 0.57 Range = 3.00 Missingness = 0	Mean = 8.63 SD = 0.53 Range = 2.00 Missingness = 4
	Mean time (ms) for correct answers		Mean = 1585.71 SD = 304.24 Range = 1654.00 Missingness = 0	Mean = 1508.96 SD = 272.53 Range = 1724.00 Missingness = 4
Verbal fluency	Total number of correct answers	The subject must name all the words they can think of within one minute based on semantic and phonetic cues.	Mean = 28.39 SD = 6.58 Range = 32.00 Missingness = 0	Mean = 29.59 SD = 7.12 Range = 43.00 Missingness = 4
VSTMBT-shape only	Total number of correct answers	The subject must recall stimuli that were shapes after a short period of retention.	Mean = 0.85 SD = 0.14 Range = 0.88 Missingness = 2	Mean = 0.86 SD = 0.17 Range = 2.31 Missingness = 10

VSTMBT-shape colour binding	Total number of correct answers	The subject must recall stimuli that were combinations of shapes and colours after a short period of retention.	Mean = 0.52 SD = 0.20 Range = 1.19 Missingness = 2	Mean = 0.54 SD = 0.24 Range = 2.19 Missingness = 11

Abbreviations: VSTMBT, visual short-term memory binding test; SD, standard deviation

Table 6.3 Statistical summary of multiple regression model testing the cross-sectional relationship between APOE genotype and Locus Coeruleus–Hippocampus (LC–HC) functional connectivity

		Baseline			Follow-up		
Model summary		R^2	$F_{(6, 121)}$	p	R^2	$F_{(6, 85)}$	p
		0.04	0.79	0.58	0.03	0.44	0.85
DV	IV	β	se	p	β	se	p
LC–HC	APOE ε4	0.06	0.05	0.19	0.02	0.06	0.71
	Age	1.301e-04	0.004	0.98	0.006	0.005	0.22
	Sex	0.002	0.05	0.98	0.03	0.06	0.63
	Years of education	-0.01	0.007	0.14	0.007	0.009	0.43
	mean FD	-0.07	1.83	0.97	1.03	1.85	0.58
	Hippocampal volume	-0.05	0.07	0.44	-0.004	0.08	0.96

Note: unstandardized coefficient (β) and standard error (se) was reported; *APOE* ε4, Apolipoprotein ε4; DV, dependent variable; IV, independent variable; FD, framewise displacement.

Table 6.4 Statistical summary of linear mixed effect model testing the longitudinal relationship between APOE genotype and Locus Coeruleus–Hippocampus (LC–HC) functional connectivity

DV	IV	*β*	*se*	*p*
LC–HC	APOE ε4	0.05	0.06	0.41
	Time	-0.07	0.04	0.11
	APOE ε4 × Time	-0.03	0.07	0.62
	Age at baseline	0.002	0.004	0.65
	Sex	0.04	0.05	0.44
	Years of education	8.75e-04	6.92e-03	0.90
	mean FD	0.26	1.53	0.86
	Hippocampal volume	0.06	0.07	0.40

Note: unstandardized coefficient (*β*) and standard error (se) was reported; *APOE* ε4, Apolipoprotein ε4; DV, dependent variable; IV, independent variable; FD, framewise displacement.

Table 6.5 Statistical summary of multiple regression model testing the cross-sectional relationship between FHD and Locus Coeruleus–Hippocampus (LC–HC) functional connectivity

		Baseline			Follow-up		
Model summary		R^2	$F_{(6, 122)}$	p	R^2	$F_{(6, 86)}$	p
		0.02	0.50	0.81	0.03	0.44	0.85
DV	IV	β	*se*	p	β	*se*	p
LC–HC	FHD	0.02	0.05	0.72	-0.005	0.05	0.93
	Age	-0.001	0.004	0.80	0.006	0.005	0.21
	Sex	-0.007	0.05	0.90	0.03	0.07	0.62
	Years of education	-0.01	0.007	0.16	0.007	0.009	0.44
	mean FD	-0.12	1.84	0.95	0.81	1.80	0.66
	Hippocampal volume	-0.05	0.07	0.45	-0.004	0.08	0.96

Note: unstandardized coefficient (β) and standard error (se) was reported; FHD, family history of dementia; DV, dependent variable; IV, independent variable; FD, framewise displacement.

Table 6.6 Statistical summary of linear mixed effect model testing the longitudinal relationship between FHD and Locus Coeruleus – Hippocampus (LC–HC) functional connectivity

DV	IV	*β*	*se*	*p*
LC–HC	FHD	-0.04	0.06	0.46
	Time	-0.09	0.04	0.04
	FHD × Time	0.04	0.06	0.51
	Age at baseline	0.001	0.004	0.78
	Sex	0.05	0.05	0.39
	Years of education	2.33e-04	0.007	0.97
	mean FD	-0.08	1.52	0.96
	Hippocampal volume	0.07	0.07	0.35

Note: unstandardized coefficient (*β*) and standard error (se) was reported; FHD, family history of dementia; DV, dependent variable; IV, independent variable; FD, framewise displacement.

Table 6.7 Statistical summary of multiple regression model testing the cross-sectional relationship between CAIDE and Locus Coeruleus – Hippocampus (LC–HC) functional connectivity

		Baseline			Follow-up		
Model summary		R^2	$F_{(3, 124)}$	p	R^2	$F_{(3, 86)}$	p
		0.01	0.48	0.70	0.01	0.31	0.82
DV	IV	β	se	p	β	se	p
LC–HC	CAIDE	0.007	0.009	0.47	0.008	0.01	0.44
	mean FD	-0.22	1.81	0.91	0.88	1.77	0.62
	Hippocampal volume	-0.06	0.06	0.32	-0.01	0.07	0.84

Note: unstandardized coefficient (β) and standard error (se) was reported; CAIDE, Cardiovascular Risk Factors, Aging and Incidence of Dementia; DV, dependent variable; IV, independent variable; FD, framewise displacement.

Table 6.8 Statistical summary of linear mixed effect model testing the longitudinal relationship between CAIDE and Locus Coeruleus – Hippocampus (LC–HC) functional connectivity

DV	IV	*β*	*se*	*p*
LC–HC	CAIDE	0.004	0.01	0.74
	Time	-0.05	0.07	0.45
	CAIDE × Time	-0.005	0.01	0.67
	mean FD	0.14	1.49	0.93
	Hippocampal volume	0.04	0.06	0.56

Note: unstandardized coefficient (*β*) and standard error (se) was reported; CAIDE, Cardiovascular Risk Factors, Aging and Incidence of Dementia; DV, dependent variable; IV, independent variable; FD, framewise displacement.

7 Appendix B – Supplementary materials in Chapter 3

7.1 Methods and Materials – The PREVENT-Dementia study

7.1.1 Individualised functional brain network construction

To overcome the inadequate field of view (FOV) and inconsistent scanning angles of the fMRI data from the PREVENT-Dementia research programme, I adapted a comprehensive brain map (Power et al., 2011) to the specific FOVs of the participants. The procedure was as follows: 1) create a brain mask for each participant; 2) multiply the individual brain mask by the original brain map (Power et al., 2011) to obtain the individualised brain map (Figure 2b); 3) set a threshold to exclude brain nodes of small size on the individualised brain map. The initial number of voxels for each brain node on the original brain map is 81. I excluded brain nodes on the individualised brain map where the number of remaining voxels was less than 80% of the initial number (80%*81=64).

7.1.2 An alternative parcellation scheme

To ensure that the network analyses were not biased by the individualised brain maps, I used an alternative parcellation scheme with fewer (node = 33 versus node = 214 in Power atlas) but key brain regions (Raichle, 2011). This parcellation method is theoretically based on a meta-analysis of seven brain networks identified in resting-state studies, and has also been used to investigate functional connectivity in different populations in previous work from our lab (Deng et al., 2023; Hu et al., 2022; Naci et al., 2018).

7.2 Supplementary Figures and Legends

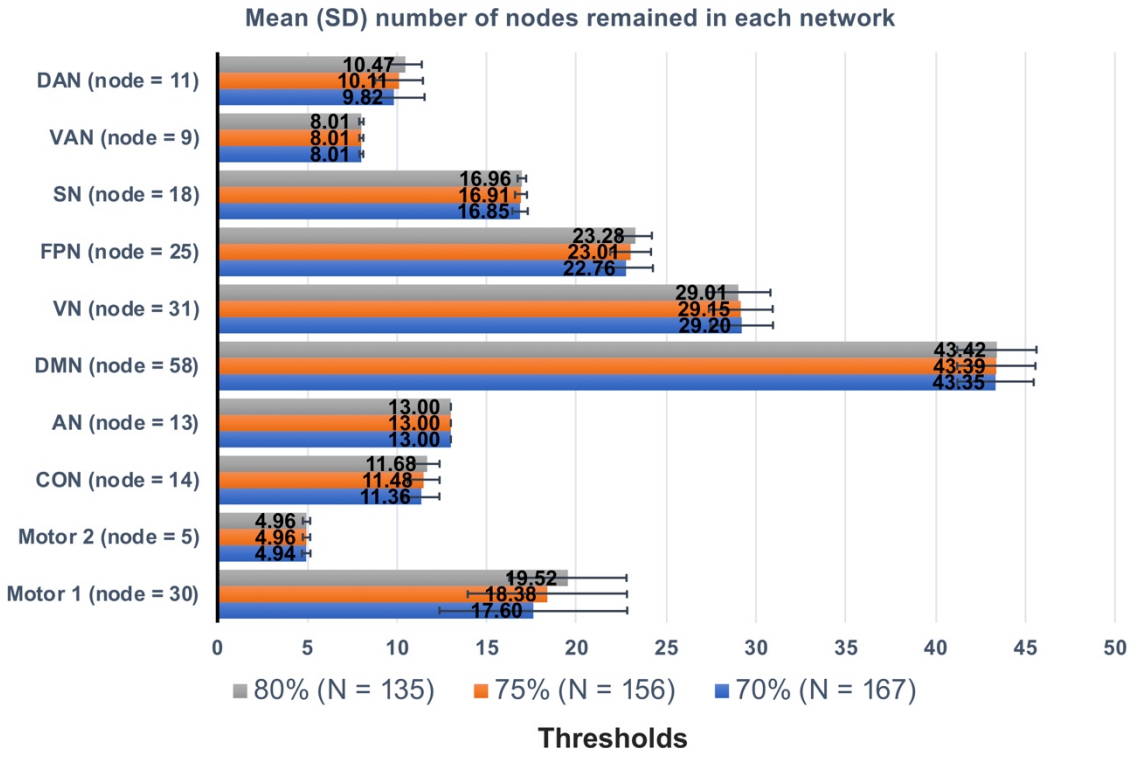

Figure 7.1 The distribution of the remained brain nodes in each network based on the Power atlas (Power et al., 2011) across the three thresholds, i.e., 70%, 75% and 80%, that I used to exclude/include participants (N = the number of included participants under each threshold). The number of remaining brain nodes was presented in the x-axis, and the 10 different networks were shown in the y-axis (node = the initial number of nodes in each network). The bar (error bar) indicates the mean (standard deviation, SD) number of nodes that remained in the specific cohort after the threshold exclusion criteria. Abbreviations: VN, visual; AN, auditory; DMN, default mode; FPN, frontal-parietal control; SN, salience; VAN, ventral attention; DAN, dorsal attention; CON, cingulo-opercular control.

7.3 Supplementary Tables

Table 7.1 Baseline differences in the global and default mode network (DMN) participation coefficient (Pc) between APOE ε4 carriers (+) and non-carriers (-) for different parcellation schemes and different participant exclusion thresholds (75% and 80%) based on the number of remained brain nodes in the Power atlas.

			Global Pc	DMN Pc
Power Atlas	70% (N=167)	APOE ε4 + (N=59)	0.29 ± 0.01	0.22 ± 0.04
		APOE ε4 - (N=106)	0.30 ± 0.01	0.23 ± 0.03
		p value	0.004	0.02
	75% (N=156)	APOE ε4 + (N=53)	0.29 ± 0.01	0.22 ± 0.04
		APOE ε4 - (N=101)	0.30 ± 0.01	0.23 ± 0.03
		p value	0.002	0.001
	80% (N=135)	APOE ε4 + (N=45)	0.29 ± 0.01	0.21 ± 0.04
		APOE ε4 - (N=88)	0.30 ± 0.01	0.23 ± 0.03
		p value	0.0004	0.0007
	The same participants as in Raichle Atlas (N=136)	APOE ε4 + (N=46)	0.29 ± 0.01	0.22 ± 0.04
		APOE ε4 - (N=88)	0.30 ± 0.01	0.23 ± 0.03
		p value	0.03	0.02
Raichle Atlas (N=136)		APOE ε4 + (N=46)	0.24 ± 0.02	0.17 ± 0.05
		APOE ε4 - (N=88)	0.24 ± 0.01	0.18 ± 0.05
		p value	0.009	0.09

Note: The shown values are mean ± standard deviation; N=number of participants included in a particular criteria; 2 participants without APOE ε4 information.

Table 7.2 Associations between the risk factors for late-life Alzheimer's disease [family history of dementia (FHD), and Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score] and global participation coefficient (Pc).

Dependent variables	Independent variables	*β*	95% CI	*t*	*p*
Global Pc	FHD	0.13	[-0.17, 0.42]	0.86	0.39
	Age	-0.06	[-0.20, 0.09]	-0.78	0.44
	Sex	0.02	[-0.29, 0.34]	0.16	0.87
	Years of education	0.03	[-0.12, 0.17]	0.36	0.72
	Mean FD	0.27	[0.13, 0.42]	3.68	0.0003
	no. of brain nodes	0.32	[0.18, 0.47]	4.32	< 0.0001
Global Pc	CAIDE	-0.11	[-0.26, 0.04]	-1.47	0.14
	Mean FD	0.27	[0.13, 0.42]	3.73	0.0003
	no. of brain nodes	0.30	[0.15, 0.44]	4.09	< 0.0001

Note: Standard coefficient β was reported. CI = confidence interval. FD = framewise displacement.

8 Appendix C – Supplementary materials in Chapter 4

8.1 Supplementary Figures and Legends

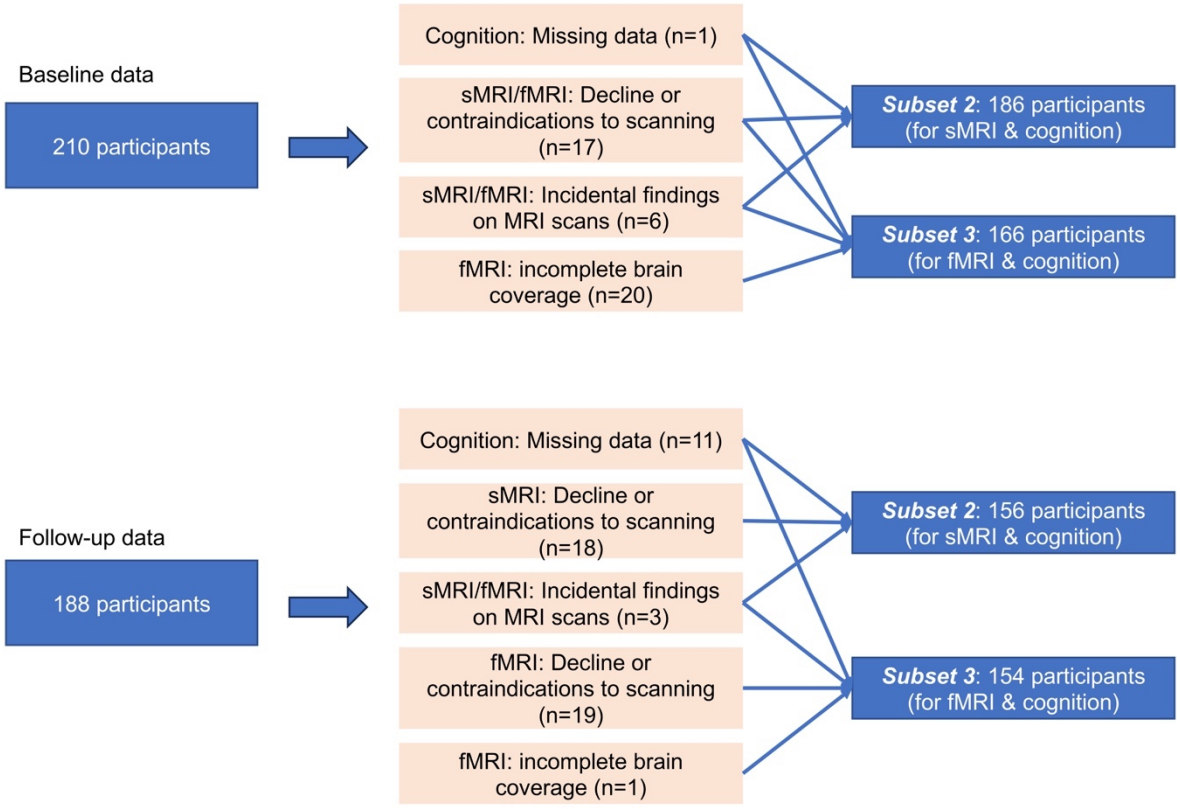

Figure 8.1 Participant inclusions for different analyses. Abbreviations: sMRI, structural magnetic resonance imaging; fMRI, functional magnetic resonance imaging.

8.2 Supplementary Tables

Table 8.1a FHD & APOE - Regression coefficients for Episodic and Relational Memory at Baseline & Follow-up.

		Baseline			Follow-up		
Model summary		R^2	$F_{(7,198)}$	p	R^2	$F_{(7,166)}$	p
		0.17	5.84	<0.0001	0.19	5.52	<0.0001
DV	IV	β (SE)		p	β (SE)		p
Episodic and Relational Memory	Specific	-0.02 (0.02)		0.36	-0.02 (0.02)		0.30
	Non-specific	0.03 (0.02)		0.18	0.03 (0.02)		0.11
	FHD	0.07 (0.13)		0.61	-0.12 (0.15)		0.41
	APOE ε4	0.26 (0.14)		0.06	0.27 (0.15)		0.07
	Age	-0.02 (0.01)		0.27	-0.005 (0.02)		0.74
	Sex	0.24 (0.14)		0.09	0.23 (0.16)		0.15
	Years of education	0.09 (0.02)		<0.0001	0.10 (0.02)		<0.0001

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; APOE ε4, Apolipoprotein ε4; FHD, family history of dementia.

Table 8.1b FHD & APOE - Regression coefficients for Episodic and Relational Memory at Baseline & Follow-up including interaction terms.

Model summary		Baseline			Follow-up		
		R^2	$F_{(11, 194)}$	p	R^2	$F_{(11, 162)}$	p
		0.18	3.88	<0.0001	0.20	3.60	0.0001
DV	IV	β (SE)		p	β (SE)		p
Episodic and Relational Memory	Specific	-0.01 (0.02)		0.57	-0.04 (0.03)		0.17
	Non-specific	0.01 (0.03)		0.67	0.02 (0.03)		0.49
	FHD	0.06 (0.13)		0.63	-0.13 (0.15)		0.39
	APOE ε4	0.25 (0.14)		0.07	0.26 (0.15)		0.09
	FHD * Specific	-0.01 (0.03)		0.86	0.03 (0.03)		0.44
	APOE ε4 * Specific	0.01 (0.03)		0.70	0.02 (0.04)		0.68
	FHD * Non-specific	-0.02 (0.04)		0.60	0.004 (0.04)		0.92
	APOE ε4 * Non-specific	0.05 (0.04)		0.18	0.02 (0.04)		0.57
	Age	-0.02 (0.01)		0.19	-0.005 (0.02)		0.75
	Sex	0.21 (0.15)		0.16	0.22 (0.16)		0.17
	Years of education	0.09 (0.02)		<0.0001	0.09 (0.02)		<0.0001

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; APOE ε4, Apolipoprotein ε4; FHD, family history of dementia.

Table 8.1c CAIDE - Regression coefficients for Episodic and Relational Memory at Baseline & Follow-up including interaction terms.

Model summary		Baseline			Follow-up		
		R^2	$F_{(5, 200)}$	p	R^2	$F_{(5, 164)}$	p
		0.05	2.04	0.07	0.08	2.76	0.02
DV	IV	β (SE)		p	β (SE)		p
Episodic and Relational Memory	CAIDE	-0.05 (0.03)		0.11	0.01 (0.03)		0.78
	Specific	-0.01 (0.02)		0.71	-0.02 (0.02)		0.32
	Non-Specific	0.04 (0.02)		0.02	0.06 (0.02)		0.003
	CAIDE * Specific	0.01 (0.01)		0.34	0.01 (0.01)		0.11
	CAIDE * Non-specific	-0.001 (0.01)		0.87	0.005 (0.01)		0.60

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CAIDE, Cardiovascular risk factors, Ageing and the Incidence of Dementia.

Table 8.2a FHD & APOE - Regression coefficients for Working and Short-Term (single-feature) Memory at Baseline & Follow-up

Model summary		Baseline			Follow-up		
		R^2	$F_{(7, 198)}$	p	R^2	$F_{(7, 166)}$	p
		0.05	1.44	0.19	0.05	1.36	0.23
DV	IV	β (SE)		p	β (SE)		p
Working and Short-Term (single-feature) Memory	Specific	0.02 (0.02)		0.22	0.01 (0.02)		0.57
	Non-specific	0.01 (0.02)		0.78	-0.03 (0.02)		0.17
	FHD	0.08 (0.14)		0.59	-0.02 (0.16)		0.89
	APOE ε4	<-0.001 (0.15)		1.00	0.22 (0.16)		0.19
	Age	-0.02 (0.02)		0.15	-0.02 (0.02)		0.23
	Sex	-0.20 (0.16)		0.21	-0.29 (0.17)		0.09
	Years of education	0.04 (0.02)		0.10	-0.003 (0.02)		0.90

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable: IV, independent variable; APOE ε4, Apolipoprotein ε4; FHD, family history of dementia.

Table 8.2b FHD & APOE - Regression coefficients for Working and Short-Term (single-feature) Memory at Baseline & Follow-up including interaction terms.

Model summary		Baseline			Follow-up		
		R^2	$F_{(11, 194)}$	p	R^2	$F_{(11, 162)}$	p
		0.06	1.08	0.38	0.08	1.29	0.23
DV	IV	β (SE)		p	β (SE)		p
Working and Short-Term (single-feature) Memory	Specific	0.03 (0.03)		0.27	0.01 (0.03)		0.81
	Non-specific	0.02 (0.03)		0.51	-0.07 (0.03)		0.04
	FHD	0.08 (0.14)		0.59	-0.03 (0.16)		0.87
	APOE ε4	0.01 (0.15)		0.93	0.19 (0.16)		0.24
	FHD * Specific	0.003 (0.03)		0.94	0.01 (0.04)		0.80
	APOE ε4 * Specific	-0.03 (0.04)		0.35	-0.01 (0.04)		0.83
	FHD * Non-specific	0.002 (0.04)		0.97	0.09 (0.05)		0.06
	APOE ε4 * Non-specific	-0.04 (0.04)		0.39	-0.001 (0.05)		0.99
	Age	-0.02 (0.02)		0.21	-0.02 (0.02)		0.30
	Sex	-0.16 (0.16)		0.31	-0.33 (0.17)		0.06
	Years of education	0.04 (0.02)		0.12	-0.004 (0.02)		0.86

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; APOE ε4, Apolipoprotein ε4; FHD, family history of dementia.

Table 8.2c CAIDE - Regression coefficient for Working and Short-Term (single-feature) Memory at Baseline & Follow-up

Model summary		Baseline			Follow-up		
		R^2	$F_{(3, 202)}$	p	R^2	$F_{(3, 166)}$	p
		0.02	1.25	0.29	0.02	0.89	0.45
DV	IV	β (SE)		p	β (SE)		p
Working and Short-Term (single-feature) Memory	CAIDE	-0.03 (0.03)		0.25	-0.001 (0.03)		0.98
	Specific	0.03 (0.02)		0.11	0.01 (0.02)		0.63
	Non-Specific	0.01 (0.02)		0.57	-0.04 (0.02)		0.11

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CAIDE, Cardiovascular risk factors, Ageing and the Incidence of Dementia.

Table 8.2d CAIDE - Regression coefficient for Working and Short-Term (single-feature) Memory at Baseline & Follow-up including interaction terms.

		Baseline			Follow-up		
Model summary		R^2	$F_{(5, 200)}$	p	R^2	$F_{(5, 164)}$	p
		0.03	1.07	0.38	0.02	0.60	0.70
DV	IV	β (SE)		p	β (SE)		p
Working and Short-Term (single-feature) Memory	CAIDE	-0.03 (0.03)		0.34	0.001 (0.03)		0.99
	Specific	0.03 (0.02)		0.10	0.01 (0.02)		0.62
	Non-Specific	0.01 (0.02)		0.63	-0.04 (0.02)		0.12
	CAIDE * Specific	0.01 (0.01)		0.33	0.004 (0.01)		0.61
	CAIDE * Non-specific	0.01 (0.01)		0.51	-0.003 (0.01)		0.71

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CAIDE, Cardiovascular risk factors, Ageing and the Incidence of Dementia.

Table 8.3a FHD & APOE - Regression coefficient values for Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory at Baseline & Follow-up

Model summary		Baseline			Follow-up		
		R^2	$F_{(7, 198)}$	p	R^2	$F_{(7,166)}$	p
		0.08	2.39	0.02	0.04	0.91	0.50
DV	IV	β (SE)		p	β (SE)		p
Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory	Specific	0.001 (0.02)		0.94	0.004 (0.02)		0.83
	Non-specific	0.03 (0.02)		0.10	0.02 (0.02)		0.51
	FHD	-0.21 (0.14)		0.13	0.20 (0.16)		0.20
	APOE ε4	-0.09 (0.15)		0.53	-0.19 (0.16)		0.25
	Age	-0.04 (0.01)		0.006	-0.03 (0.02)		0.11
	Sex	0.22 (0.15)		0.16	0.18 (0.17)		0.29
	Years of education	-0.01 (0.02)		0.55	0.01 (0.02)		0.77

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; APOE ε4, Apolipoprotein ε4; FHD, family history of dementia.

Table 8.3b CAIDE - Regression coefficient for Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory at Baseline & Follow-up

Model summary		Baseline			Follow-up		
		R^2	$F_{(3, 202)}$	p	R^2	$F_{(3,166)}$	p
		0.05	3.84	0.01	0.02	1.24	0.30
DV	IV	β (SE)		p	β (SE)		p
Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory	CAIDE	-0.08 (0.03)		0.006	-0.05 (0.03)		0.07
	Specific	-0.006 (0.02)		0.70	-0.003 (0.02)		0.88
	Non-Specific	0.02 (0.02)		0.21	0.008 (0.02)		0.70

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CAIDE, Cardiovascular risk factors, Ageing and the Incidence of Dementia.

Table 8.3c CAIDE - Regression coefficient for Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory at Baseline & Follow-up including interaction terms.

Model summary		Baseline			Follow-up		
		R^2	$F_{(5, 200)}$	p	R^2	$F_{(5, 164)}$	p
		0.07	3.11	0.01	0.03	0.92	0.47
DV	IV	β (SE)		p	β (SE)		p
Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory	CAIDE	-0.07 (0.03)		0.01	-0.06 (0.03)		0.08
	Specific	-0.01 (0.02)		0.54	-0.001 (0.02)		0.94
	Non-Specific	0.02 (0.02)		0.24	0.01 (0.02)		0.63
	CAIDE * Specific	-0.01 (0.01)		0.16	0.04 (0.01)		0.58
	CAIDE * Non-specific	0.01 (0.01)		0.12	-0.01 (0.01)		0.40

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; CAIDE, Cardiovascular risk factors, Ageing and the Incidence of Dementia.

Table 8.4 Brain structural health - Regression coefficients for Episodic and Relational Memory at Baseline & Follow-up

		Baseline			Follow-up		
Model summary		R^2	$F_{(9, 176)}$	*p*	R^2	$F_{(9, 146)}$	*p*
		0.19	4.50	<0.0001	0.24	5.16	<0.0001
DV	IV	β	SE	*p*	β	SE	*p*
Episodic and Relational Memory	Specific	-0.02	0.02	0.20	-0.03	0.02	0.16
	Non-specific	0.04	0.02	0.06	0.04	0.02	0.05
	TGMV	-3.36e-06	3.00e-06	0.26	-2.56e-06	3.31e-06	0.44
	TGMV * Specific	-1.13e-07	2.89e-07	0.70	-1.35e-07	3.69e-07	0.72
	TGMV * Non-specific	5.67e-08	4.59e-07	0.90	1.41e-08	4.79e-07	0.98
	Age	-0.01	0.01	0.33	-0.02	0.02	0.27
	Sex	0.21	0.19	0.27	0.21	0.21	0.32
	Years of education	0.10	0.02	<0.0001	0.12	0.02	<0.0001
	TICV	1.65e-06	1.00e-06	0.10	1.33e-06	1.13e-06	0.24

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; TGMV, total grey matter volume; TICV, total intracranial volume

Table 8.5 Brain structural health - Regression coefficients for Working and Short-Term (single-feature) Memory at Baseline & Follow-up

Model summary		Baseline			Follow-up		
		R^2	$F_{(9, 176)}$	*p*	R^2	$F_{(9, 146)}$	*p*
		0.05	1.04	0.41	0.07	1.29	0.25
DV	IV	β	SE	*p*	β	SE	*p*
Working and Short-Term (single-feature) Memory	Specific	0.02	0.02	0.43	0.02	0.02	0.33
	Non-specific	0.007	0.02	0.73	-0.04	0.02	0.13
	TGMV	3.44e-07	3.28e-06	0.92	-8.17e-07	3.61e-06	0.82
	TGMV * Specific	6.06e-08	3.16e-07	0.85	7.33e-07	4.02e-07	0.07
	TGMV * Non-specific	3.32e-08	5.01e-07	0.95	-2.32e-07	5.22e-07	0.66
	Age	-0.02	0.02	0.24	-0.02	0.02	0.21
	Sex	-0.11	0.20	0.60	-0.34	0.23	0.13
	Years of education	0.04	0.02	0.10	0.005	0.03	0.84
	TICV	3.32e-07	1.10e-06	0.76	2.36e-07	1.23e-06	0.85

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; TGMV, total grey matter volume; TICV, total intracranial volume

Table 8.6 Brain structural health - Regression coefficients for Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory at Baseline & Follow-up

Model summary		Baseline			Follow-up		
		R^2	$F_{(9, 176)}$	*p*	R^2	$F_{(9, 146)}$	*p*
		0.08	1.71	0.09	0.05	0.86	0.57
DV	IV	β	SE	*p*	β	SE	*p*
Verbal, Visuospatial Functions, and Short-Term (conjunctive) Memory	Specific	0.01	0.02	0.55	-0.001	0.02	0.95
	Non-specific	0.04	0.02	0.10	0.02	0.02	0.49
	TGMV	-7.56e-07	3.32e-06	0.82	4.44e-06	3.61e-06	0.22
	TGMV * Specific	7.78e-08	3.19e-07	0.81	-5.38e-07	4.02e-07	0.18
	TGMV * Non-specific	-7.99e-07	5.06e-07	0.12	7.99e-07	5.22e-07	0.13
	Age	-0.05	0.02	0.004	-0.02	0.02	0.26
	Sex	0.22	0.21	0.28	0.27	0.23	0.23
	Years of education	-0.03	0.02	0.26	-0.002	0.03	0.94
	TICV	3.72e-07	1.11e-06	0.74	-1.04e-06	1.23e-06	0.40

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; TGMV, total grey matter volume; TICV, total intracranial volume

Table 8.7 Brain functional health - Regression coefficients for Episodic and Relational Memory at Baseline & Follow-up

Model summary		Baseline			Follow-up		
		R^2	$F_{(8, 157)}$	*p*	R^2	$F_{(8, 145)}$	*p*
		0.21	5.08	<0.0001	0.25	5.94	<0.0001
DV	IV	β	SE	*p*	β	SE	*p*
Episodic and Relational Memory	Specific	-0.02	0.02	0.33	-0.02	0.02	0.19
	Non-specific	0.03	0.02	0.20	0.04	0.02	0.04
	Global Pc	-13.10	5.04	0.01	0.51	5.80	0.93
	Global Pc * Specific	0.75	1.00	0.45	0.29	1.39	0.84
	Global Pc * Non-specific	-1.93	1.48	0.19	1.84	1.30	0.16
	Age	-0.01	0.01	0.39	-0.02	0.02	0.29
	Sex	0.20	0.15	0.20	0.19	0.17	0.27
	Years of education	0.10	0.02	<0.0001	0.12	0.02	<0.0001

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; Pc, participation coefficient.

Table 8.8 Brain functional health - Regression coefficients for Working and Short-Term (single-feature) Memory at Baseline & Follow-up

Model summary		Baseline			Follow-up		
		R^2	$F_{(8, 157)}$	*p*	R^2	$F_{(8, 145)}$	*p*
		0.08	1.74	0.09	0.08	1.59	0.13
DV	IV	β	SE	*p*	β	SE	*p*
Working and Short-Term (single-feature) Memory	Specific	0.01	0.02	0.54	0.01	0.02	0.56
	Non-specific	0.02	0.02	0.32	-0.04	0.02	0.11
	Global Pc	6.41	5.21	0.22	-7.60	6.31	0.23
	Global Pc * Specific	-0.14	1.04	0.89	-1.52	1.51	0.32
	Global Pc * Non-specific	3.45	1.54	0.03	2.91	1.41	0.04
	Age	-0.02	0.01	0.30	-0.01	0.02	0.45
	Sex	-0.20	0.16	0.21	-0.32	0.18	0.08
	Years of education	0.03	0.02	0.27	0.003	0.03	0.91

Note: unstandardized coefficients β and standard error (SE) were reported. DV, dependent variable; IV, independent variable; Pc, participation coefficient.

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