Examining the Neural Correlates of Cognitive and Social Activity Levels in Middle-Aged and Older Adults



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Abstract

As populations around the world are rapidly ageing, there is an urgent need to identify modifiable determinants of brain health in late life. Cognitive and social activities represent potential candidates, particularly as they have previously been linked to a lower risk of cognitive decline and dementia. The aim of this thesis was therefore to evaluate whether cognitive and social activities associate with magnetic resonance imaging (MRI) markers of brain structure and functional connectivity and performance on neuropsychological assessments.

A systematic review and meta-analysis were first conducted of previous MRI studies, to evaluate whether cognitive and social activities relate to imaging indices of brain structure. The review suggested that when combined, higher activity levels were linked to greater white matter volume, fewer white matter lesions and greater hippocampal volume.

With the review largely inconclusive about the *independent* associations of cognitive and social activities, *late life activity levels* were next examined in relation to brain integrity and cognitive function. In a cross-sectional analysis of Whitehall II data, cognitive activity was the only activity to associate with cognition (global and executive function), whereas social activities were related to total grey matter volume, without any cognitive correlates.

Given that a cross-sectional design is insensitive to *changes* in activity levels that occur over time, the Whitehall II dataset was revisited in order to evaluate whether *trajectories* of leisure activities relate to the ageing brain. Between mid-life and late life, a curvilinear pattern of change in activities was observed. Level and change in *cognitive activities* also associated with global cognition, executive function, memory and processing speed, while social activities related to executive function, only. The links with brain structure and functional connectivity, however, remained small.

Considering that composite measures of leisure activities are non-specific indices, the next objective was to assess whether *particular activities* play a significant role in maintaining the brain in late life. Examining data from the UK Biobank study, weekly leisure-time computer use during mid-life and late life was linked to performance on multiple tests (e.g. fluid intelligence and prospective memory) with mid-life computer use further related to putamen volume. Late life educational classes demonstrated links with higher fluid intelligence, while mid-life attendance at a sports club or gym was related to sensorimotor connectivity.

Overall, this thesis provides evidence to suggest that leisure activities – cognitive activities in particular – are consistently linked to late life cognition. However, associations with measurable brain structure and functional connectivity were found to be scarce.

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Oxford. This thesis contains approximately 42,714 words.

Table of Contents

TABLE OF CONTENTS 3
ACKNOWLEDGEMENTS 8
DEDICATION 9
LIST OF ABBREVIATIONS 10
LIST OF FIGURES 12
LIST OF TABLES 14
LIST OF PUBLICATIONS AND PRESENTATIONS 15

INTRODUCTION 16
1.1 POPULATION AGEING 16
1.2 LEISURE ACTIVITIES AS PROTECTIVE FACTORS 18
1.3 PRINCIPLES OF MAGNETIC RESONANCE IMAGING (MRI) 27
1.3.1 MRI Measures of Grey Matter 29
1.3.2 MRI insights into the Ageing Grey Matter 33
1.3.3 MRI Measures of White Matter 34
1.3.4 MRI insights into the Ageing White Matter 39
1.3.5 MRI Measures of Functional Connectivity 40
1.3.6 MRI Insights into Functional Connectivity and Ageing 44
1.4 PLASTICITY IN THE AGEING BRAIN 46
1.5 AIMS 47

CHAPTER 2: A SYSTEMATIC REVIEW AND META-ANALYSIS ON THE RELATIONSHIP BETWEEN LEISURE ACTIVITIES AND BRAIN STRUCTURE IN HEALTHY OLDER ADULTS 49
ABSTRACT 49
2.1 INTRODUCTION 51
2.1.1 Aims 52
2.2 METHODS 53
2.2.1 Data Sources 53
2.2.2 Inclusion Criteria 53
2.2.3 Study Identification and Selection 54
2.2.4 Data Extraction 55
2.2.5 Quality Assessment 57
2.3 RESULTS 58

2.3.1. Grey Matter (GM). 61
2.3.1.1 Global GM Volume 61
2.3.1.2 Local GM Volume 63
2.3.2 White Matter (WM) 67
2.3.2.1 Global WM Volume 67
2.3.2.2 Local WM Volume 69
2.3.2.3 Global WM Lesions 70
2.3.2.4 WMM 72
2.4 DISCUSSION 75
2.4.1 Summary of Findings 75
2.4.2 Do Socio-Intellectual Activities Support Neural Mechanisms? 76
2.4.3 Neurobiological Mechanisms 77
2.4.4 Methodological Consideration: Demographics and Generalizability 78
2.4.5 Methodological Considerations: Study Design and Directionality 79
2.4.6 Methodological Considerations: Measurements of Leisure Activities and Risk of Bias 80
2.4.7 Methodological Considerations: Defining and Distinguishing between Cognitive and Social Activities 83
2.5 CONCLUSION 87

CHAPTER 3: ASSOCIATIONS BETWEEN LATE LIFE ACTIVITY LEVELS, BRAIN STRUCTURE, FUNCTIONAL CONNECTIVITY AND COGNITION IN THE WHITEHALL II COHORT 89
ABSTRACT 89
3.1 INTRODUCTION. 91
3.1.1 Aims 92
3.2 METHODS 92
3.2.1 Sample Characteristics 92
3.2.2 Inclusion/Exclusion Criteria 93
3.2.3 Cognitive and Social Activity Levels 93
3.2.4 Cognitive Function 94
3.2.5 Demographic and Health Variables 95
3.2.6 MRI Data Acquisition and Pre-processing 96
3.2.6.1 MRI Data Acquisition 96
3.2.6.2 MRI Data Pre-processing 97
3.2.7 Statistical Analyses 101
3.2.7.1 Comparisons of Included and Excluded Participants 101

3.2.7.2 Main Analysis 101
3.3 RESULTS 103
3.3.1 Sample Characteristics 103
3.3.2 Comparison of Included and Excluded Participants 105
3.3.2 Activities and Cognitive Function 106
3.3.3 Activities and Grey Matter 106
3.3.4 Activities and White Matter 109
3.3.5 Activities and Resting-state Functional Connectivity 110
3.4 DISCUSSION 111
3.4.1 Cognitive Activities 111
3.4.2 Social Activities 105
3.5 STRENGTHS AND LIMITATIONS 118
3.6 CONCLUSION 119

CHAPTER 4: TRAJECTORIES OF ACTIVITY LEVELS BETWEEN MID- AND LIFE LATE AND THEIR RELATIONSHIP WITH BRAIN INTEGRITY IN THE WHITEHALL II COHORT 120
ABSTRACT 120
4.1 INTRODUCTION 122
4.1.1 Aims 123
4.2 METHODS 124
4.2.1 Sample Characteristics 124
4.2.2 Inclusion/Exclusion Criteria 125
4.2.3 Cognitive and Social Activity Levels 125
4.2.4 Cognitive Function 126
4.2.5 Demographic and Health Variables 126
4.2.6 MRI Data Acquisition and Pre-processing 127
4.2.7 Missing Data 127
4.2.8 Statistical Analyses 127
4.2.8.1 Comparisons of Included and Excluded Participants 127
4.2.8.2 Trajectory Analyses 127
4.2.8.3 Neuroimaging Analyses 130
4.3 RESULTS 130
4.3.1 Sample Characteristics 132
4.3.2 Comparison of Included and Excluded Participants. 133
4.3.3 Cognitive and Social Activity Trajectories 135
4.3.4 Activities and Cognitive Function 138

4.3.5 Activities and Grey Matter . . . 139
4.3.6 Activities and White Matter . . . 139
4.3.7 Activities and Resting-state Functional Connectivity . . . 139
4.4 DISCUSSION . . . 142
4.5 STRENGTHS AND LIMITATIONS . . . 148
4.6 CONCLUSION . . . 150

CHAPTER 5: ASSOCIATIONS BETWEEN INDIVIDUAL ACTIVITIES DURING MID-LIFE AND LATE LIFE AND MRI MEASURES OF THE AGEING BRAIN IN THE UK BIOBANK COHORT . . . 152
ABSTRACT . . . 152
5.1 INTRODUCTION. . . . 154
5.1.1 Aims . . . 155
5.2 METHODS . . . 156
5.2.1 Sample Characteristics . . . 156
5.2.2 Inclusion and Exclusion Criteria . . . 157
5.2.3 Activities . . . 158
5.2.4 Cognitive Function . . . 159
5.2.5 Demographic and Health Variables . . . 161
5.2.6 MRI Data Acquisition and Pre-processing . . . 163
5.2.6.1 MRI Data Acquisition . . . 163
5.2.6.2 MRI Data Pre-processing . . . 163
5.2.7 Statistical Analyses . . . 167
5.2.7.1 Comparisons of Included and Excluded Participants . . . 167
5.2.7.2 Main Analysis . . . 167
5.3 RESULTS . . . 169
5.3.1 Sample Characteristics . . . 170
5.3.2 Comparison of Included and Excluded Participants . . . 171
5.3.3 Associations Between Activities, Brain Structure, Functional Connectivity and Cognitive Function . . . 171
5.3.3.1 Cognitive function . . . 171
5.3.3.1.1 Mid-life Activity Levels . . . 171
5.3.3.1.2 Late life Activity Levels . . . 172
5.3.3.2 Structural MRI . . . 175
5.3.3.2.1 Mid-life Activity Levels . . . 175
5.3.3.2.2 Late life Activity Levels . . . 175
5.3.3.3 Functional MRI . . . 177

5.3.3.3.1 Mid-life Activity Levels 177
5.3.3.3.2 Late life Activity Levels 178
5.4 DISCUSSION 178
5.5 STRENGTHS AND LIMITATIONS 184
5.6 CONCLUSION 186

CHAPTER 6: CONCLUSIONS AND FUTURE DIRECTIONS 188
6.1 Revisiting the Aims of This Thesis 188
6.2 Conclusions 190
6.2.1 Activities Are Linked With Late Life Cognition 190
6.2.2 Minimal Links Between Activities and MRI Indices 193
6.3 Final Methodological Considerations 195
6.3.1 Study Design and Directionality 195
6.3.2 Measurements of Leisure Activities 197
6.3.3 Definitions of Leisure Activities 198
6.3.4 Demographics and Generalizability 202
6.4 Suggestions for Further Work 203
6.5 Concluding Remarks 204
REFERENCES 205
APPENDICES 230

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Dedication

A lifelong scholar, passionate mentor and beloved friend,
this thesis is dedicated to the memory of
Diana Markerink-Mangir.

List of Abbreviations

ACE-III	Addenbrooke's Cognitive Examination Revised
AD	Axial Diffusivity
AIC	Akaike Information Criteria
AN	Auditory Network
APOE4	Apolipoprotein E ε4
B	Unstandardized Regression Coefficient
β	Standardized Regression Coefficient
BET	Brain Extraction Tool
BGN	Basal Ganglia Network
BIANCA	Brain Intensity Abnormality Classification Algorithm
BIC	Bayesian Information Criteria
BLRT	Bootstrapped Likelihood Ratio Test
BMI	Body Mass Index
BP	Blood Pressure
CA	Cognitive Activity
CANTAB	Cambridge Neuropsychological Test Automated Battery
CES-D	Center for Epidemiologic Studies Depression Scale
CFI	Comparative Fit Index
CHAMPS	Community Healthy Activities Model Program for Seniors
CHD	Coronary Heart Disease
CI	Confidence Intervals
CN	Cerebellar Network
CSF	Corticospinal Fluid
CT	Cognitive Training
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
ECN	Executive Control Network
FA	Fractional Anisotropy
FAST	FMRIB's Automated Segmentation Tool
FDR	False Discovery Rate
FLAIR	Fluid Attenuated Inversion Recovery
FLIRT	FMRIB's Linear Image Registration Tool
FMRI	Functional Magnetic Resonance Imaging
FMRIB	Oxford Centre for Functional Magnetic Resonance Imaging of the Brain
FNIRT	FMRIB's Non-Linear Image Registration Tool
FOV	Field of View
FPN	Fronto-parietal Network
FSL	FMRIB's Software Library
FWHM	Full Width at Half Maximum
GM	Grey Matter

HVLT-R	Hopkins Verbal Learning Test Revised
ICA	Independent Component Analysis
ICD	International Classification of Diseases
ICV	Intracranial Volume
LCGM	Latent Class Growth Model
LGCM	Latent Growth Curve Model
LRT-RT	Lo-Mendell-Rubin Likelihood Ratio Test
MAP	Mean Arterial Pressure
MCI	Mild Cognitive Impairments
MD	Mean Diffusivity
MELODIC	Multivariate Exploratory Linear Optimized Decomposition into Independent Components
MMSE	Mini-Mental State Examination
MNI	Montreal Neurological Institute
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
NODDI	Neurite Orientation Dispersion and Density Imaging
PET	Positron Emission Tomography
PSQI	Pittsburgh Sleep Quality Index
RAVLT	Rey Auditory Verbal Learning Test
RCF	Rey Complex Figure
RCT	Randomised-Controlled Trial
RD	Radial Diffusivity
RDI	Recognition Discrimination Index
RMSEA	Root Mean Square Error of Approximation
ROI	Region of Interest
SE	Standard Error
SMN	Sensorimotor Network
SSA-BIC	Sample Size Adjusted BIC
SPECT	Single-Photon Emission Computed Tomography
TBSS	Tract-Based Spatial Statistics
TE	Echo Time
TFCE	Threshold-Free Cluster Enhancement
TLI	Tucker-Lewis Index
TMT	Trail Making Test
TPN	Temporo-parietal Network
TR	Repetition Time
VBA	Voxel-Based Analysis
VBM	Voxel-Based Morphometry
VN	Visual Network
WIN	Wellcome Centre for Integrative Neuroimaging
WM	White Matter

List of Figures

1.1 Overview of MRI scanner hardware.

1.2 Steps involved in the pre-processing of T1-weighted images for ROI and VBM analyses.

1.3 Schematic diagram of the diffusion tensor model.

1.4 Example of large-scale resting-state networks identified using ICA.

2.1 Flow chart of study selection and exclusion.

2.2 Effect sizes (correlation coefficient) for total GM volume: No significant association between activity levels and global GM volume.

2.3 Cognitive and social activity levels and global grey matter volume: a funnel plot of standard errors plotted against Fisher's Z.

2.4 Effect sizes (correlation coefficient) for hippocampal volume: Higher levels of leisure activities are associated with greater hippocampal volume.

2.5 Leisure activities and hippocampal volume: a funnel plot of standard errors plotted against Fisher's Z.

2.6 Effect sizes (correlation coefficient) for total WM volume: a positive relationship between cognitive and social activity levels and whole-brain WM volume.

2.7 Cognitive and social activity participation and global white matter volume: a funnel plot of standard errors plotted against Fisher's Z

2.8 Effect sizes (correlation coefficient) for global WM lesions: Higher activity levels are related to a reduction in whole-brain WM lesion volume.

2.9 Activity participation and global white matter lesions: a funnel plot of standard errors plotted against Fisher's Z.

2.10 Schematic diagram outlining the proposed neurobiological mechanisms that may support associations between activities and brain reserve and cognition, in old age.

2.11 Schematic diagrams representing the different methods used to operationalize leisure activities.

3.1 ICA spatial maps for components representing the ECN, DMN and FPN, overlaid on an MNI152 standard template of the brain.

3.2 VBM results.

4.1 A timeline of the study phases and key variables included in the present analyses.

4.2 Estimated means of cognitive activity levels over time.

4.3 Estimated means of social activity levels over time.

4.4 Results of post-hoc analyses examining additional resting-state networks.

5.1 A timeline of the study assessments and variables of interest examined in the current analyses.

5.2 Dot-and-whisker plots to show associations between mid-life and late-life computer use and alphanumeric trail making (standardized beta coefficients), numeric trail making (standardized beta coefficients) and prospective memory performance (Odds ratio).

5.3 Diagram to highlight the left putamen, which was positively associated with mid-life computer use.

5.4 Dot-and-whisker plots of standardized beta coefficients comparing the effect size of weekly computer use against all other activities.

5.5 Mid-life sports club and gym attendance was associated with stronger connectivity (red lines) between the sensorimotor network (node 12) and lateral visual network (node 19) and cerebellar network (node 15).

6.1 Revisiting the methods used in the literature to probe the relationship between activities and the ageing brain.

List of Tables

1.1 A table to summarize recent systematic reviews examining the association between cognitive activities, cognitive function and dementia risk.

1.2 A table to summarize recent systematic reviews investigating association between social activities, cognitive function and dementia risk.

1.3 A table summarizing common metrics derived from a diffusion tensor model.

2.1 Activity definitions.

2.2 Sample characteristics and design of included studies.

2.3 Cross-sectional MRI studies that have investigated the association between CA and SA levels and global GM volume.

2.4 Cross-sectional and longitudinal MRI studies that have investigated the relationship between activity participation and local GM volume.

2.5 Findings of cross-sectional MRI studies that have addressed the relationship between activity levels and global WM volume.

2.6 The results of cross-sectional MRI studies that have assessed associations between activity levels and region-specific measures of WM volume.

2.7 Findings of cross-sectional and longitudinal studies that have investigated whether activity levels are related to whole-brain WM lesions.

2.8 Results of cross-sectional and longitudinal DTI studies to have examined associations between cognitive and social activity participation and WMM.

3.1 Participant characteristics.

3.2 Coordinates of the cluster that positively correlated with social activity levels in the voxel-wise analyses of GM volume.

3.3 A summary of the linear regression results

4.1 Characteristics of the analytical sample.

4.2 Model fit indices for unconditional latent growth curve models.

4.3 As the latent growth curve analyses identified the quadratic pattern of cognitive activity as the 'best fitting pattern of growth', we report the results of unconditional quadratic latent class growth models.

5.1 Participant characteristics.

List of Publications and Presentations

Publications

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CHAPTER 1
Introduction

Contents

1.1 Population Ageing 16

1.2 Leisure Activities as Protective Factors 18

1.3 Principles of Magnetic Resonance Imaging 27

1.3.1 MRI Measures of Grey Matter 29

1.3.2 MRI insights into the Ageing Grey Matter 33

1.3.4 MRI Measures of White Matter 34

1.3.5 MRI insights into the Ageing White Matter 39

1.3.6 MRI Measures of Functional Connectivity 40

1.3.7 MRI Insights into Functional Connectivity and Ageing . . . 44

1.4 Plasticity in the Ageing Brain 46

1.5 Aims 47

1.1 Population ageing

By 2050, the total number of older adults (i.e. individuals ≥ 60 years old) worldwide is expected to reach 2.1 billion individuals (Prince et al., 2015). While improvements in life expectancy is a significant achievement of the 21st century, it is no secret that population ageing represents a major societal challenge (World Health Organization, 2015). This is because older adults are often at a greater risk of developing certain health conditions than their younger counterparts. For instance, an individual aged 90 or older has 25 times the risk of developing dementia compared to an individual in their late 60s (Brayne, 2007; Yip et al., 2006). Alarmingly, whole population rates of dementia, such as Alzheimer's disease, are projected to triple by 2050 as a consequence of population ageing (Prince et al., 2015). Given that clinical trials are yet to identify an effective treatment for Alzheimer's disease (Schneider et al., 2014), there is an urgent need to invest in *preventive* strategies (Crous-Bou

et al., 2017). Preventive strategies include the practice of identifying and targeting *modifiable* determinants of disease development (Crous-Bou et al., 2017). Promisingly, a recent review commissioned by the Lancet has suggested that up to a third of all dementia cases could be prevented if 7 key *modifiable* factors were targeted (Livingston et al., 2017), spurring an interest into lifestyle-based interventions aimed at reducing dementia risk.

It is now well established that even among healthy individuals cognitive function declines with age (Harada et al., 2013; Hedden and Gabrieli, 2004; Park and Reuter-Lorenz, 2009). Non-pathological age-related cognitive changes are typically found for executive function (e.g. inhibitory function), memory (e.g. working and long-term memory), and processing speed (Hedden and Gabrieli, 2004). These cognitive domains are essential to the daily functioning, where executive function (also known as "cognitive/executive control") refers to a set of top down processes such as attention, planning and self-monitoring (Diamond, 2013; Harada et al., 2013); memory is the ability to encode, store and recall information (Bisaz et al., 2014). Processing speed is the rate at which cognitive and motor tasks are performed (Eckert et al., 2010). Declines in these abilities can have far-reaching implications, including a poorer ability to conduct daily activities, such as driving (Harada et al., 2013). Notably, age-related decline does not affect all aspects of cognition, with vocabulary, semantic memory and world knowledge relatively intact across the lifespan (e.g. Harada et al., 2013; Hedden and Gabrieli, 2004). Cognitive decline is also no longer considered to be an inevitable part of ageing, as some individuals exhibit minimal or no decline even in the advanced stages of life (Glisky, 2007). A priority of global policy initiatives is to prolong the years of life lived in good health and independence among older adults (World Health Organization, 2015). It is therefore imperative to understand whether modifiable factors hinder or prevent the development of dementia and, more

generally, whether they hold importance in supporting cognitive function among this growing demographic.

1.2 Leisure activities as protective factors

Evidence is growing for an association between cognitive and socially active lifestyles and late life cognitive health (Evans et al., 2018; Matyas et al., 2019; Wang et al., 2012). For instance, a recent review of five published systematic reviews identified cognitively stimulating activities (e.g. reading, computer use) as consistently associated with a reduced risk of developing mild cognitive impairments (MCI) and Alzheimer's disease (Matyas et al., 2019). Furthermore, cognitive activities appear to be predictive of better performance on tests of overall cognition, as well as executive function, memory, processing speed and language (see Table 1.1, Matyas et al., 2019). Matyas and colleagues (2019), however, cautioned that there were substantial differences in the effect sizes reported by different reviews, leaving future studies to better delineate these estimates. Late life social disengagement is another dementia risk factor highlighted in the seminal paper by Livingston and colleagues (2017), which further suggested that if social isolation was successfully targeted, there could be up to a 2.3% reduction in the incidence of dementia. Other systematic reviews and meta-analyses (Table 1.2) also point toward an inverse relationship between social activities (e.g. visiting friends and family; being part of a club) and dementia, with the most recent review (Evans et al., 2018) further establishing small associations between global and domain specific cognition, namely, executive function and memory. Taken together, prospective cohort findings have encouragingly suggested that leisure activities could serve as potential targets for interventions aimed at promoting cognitive health in older adults. Indeed, leisure activities lend themselves as ideal candidates, particularly as they themselves are inherently multi-modal and by definition – enjoyable. Yet observational evidence alone cannot establish whether the observed

associations translate to clinically meaningful *effects,* particularly as these studies may be confounded by reverse causation, third variable explanations or cohort effects, to name a few. We[1] next describe the findings of key randomized controlled trials (RCTs) or, where available, reviews of RCTs that have examined the effects of cognitive and social engagement on late life cognition. While physical activity has also been indicated as a potential correlate of late life cognition, this activity has been comprehensively reviewed elsewhere (Baumgart et al., 2015; Blondell et al., 2014; Sanders et al., 2019; Sofi et al., 2011) and is therefore beyond the scope of this thesis.

When it comes to cognitive activities, the RCT literature is separated into two major arms of research. The first and most abundant arm is the work that has focused exclusively on cognitive training (CT) interventions. CT involves repeatedly training one or multiple domains of cognition (e.g. executive function), through either pen-and-paper or computerized exercises, with the overarching aim to boost cognition (Gates and Valenzuela, 2010). The number of studies investigating CT as an intervention have soared over the last few years, particularly as such programmes have the potential to be far-reaching and are cost-effective to administer. Several meta-analyses have now been conducted within the field, with the evidence largely suggestive of a positive effect of CT on cognition (e.g. Gates et al., 2019; Kelly et al., 2014; Lampit et al., 2014; Mewborn et al., 2017). Examining 97 studies that included healthy and cognitively impaired older adults, Mewborn et al. (2017) found that CT lead to better global cognition, with post hoc analyses indicated that the effects were stronger for trained or closely related domains, with untrained domains demonstrating significant, albeit weaker effects. A recent Cochrane review of a smaller set of studies (n = 8) assessing computerized CT (duration = 12 – 26

[1]In order to conform to the usual tone of a scientific paper, every instance of "I"/ "my" will be substituted with "we"/ "our" herein.

weeks) in healthy older adults, conversely suggested that intervention effects were limited to episodic memory, without any effects on executive function, working memory or verbal fluency, relative to inactive controls (Gates et al., 2019). Nevertheless, it remains difficult to draw conclusions on which cognitive abilities are sensitive to the effects of CT, and whether all variants of training are beneficial for cognition (Sala et al., 2018). The heterogeneity within the literature undoubtably contributes to this 'noise', which includes differences in intervention duration and intensity, type of CT programme (e.g. commercialized versus study-specific; single-domain versus multi-domain) and differences in the sample characteristics (e.g. healthy versus cognitively impaired).

The second, smaller arm of RCT research on cognitive activities is often described with the umbrella term of 'activity engagement', with the idea here being to improve participation in already available, 'everyday' home- and community-based leisure activities (e.g. encouraging older adults to read regularly or play chess, Kelly et al., 2014). In a systematic review of 8 RCTs, Kelley and colleagues identified several patterns of results replicated across studies, with such interventions leading to better performance on tests of memory (4/8 assessments) and executive function (9/17 assessments), compared to waitlist controls. The evidence was less convincing if studies used active controls (e.g. partaking in singing classes, physical exercise), with no difference found between intervention and control participants (n. of studies = 3; Kelly et al., 2014). RCTs combining cognitive and social activities have also been developed in the same way, with the aim of exposing older adults to more group-orientated activities relative to their baseline. One pivotal example is the Experience Corps trial located in Baltimore, which is an intergenerational program that sees older adults volunteering for 15 hours per week at local schools, undertaking a range of duties including to help improve children's literacy, managing behaviour in the playground and library support (Glass, 2004). No main effects

were observed in the trial (n. of individuals =149, Carlson et al., 2008). However, when the sample was stratified based on cognitive impairment, significant post-intervention improvements in switching and verbal memory abilities were observed exclusively for participants with cognitive impairments in the intervention arm, compared to controls with cognitive impairment (Carlson et al., 2008). Significant effects on semantic and phonemic fluency have otherwise been reported following a 6-week online-delivered social intervention for older adults living in retirement communities (Dodge et al., 2015). Although the evidence using 'activity engagement' paradigms is comparably thin compared to the wealth of CT publications, the overall trends in literature provide backing for the hypothesis that activities may impact cognition. Given that there are inconsistencies between study findings, it may be worth investing in research that aims to identify the optimal frequency, intensity, duration for cognitive and social activities to yield a likely effect on late life cognition. Importantly, consistent use of active controls across studies will also provide more convincing evidence of a direct effect of these activities on cognitive function.

It is clear from our brief review that epidemiological studies have revealed major insights: including (a) identifying a link between ageing, dementia risk and cognitive decline and (b) highlighting leisure activities as a potential buffer against poor cognitive health in late life. Current RCTs are also in favour of an effect of leisure activities on cognition. A caveat of the above discussed literature is that primary outcomes have been restricted to performance on neuropsychological tests or a clinical diagnosis of dementia, without assessing the underlying mechanisms driving the associations of either (a) or (b). Magnetic resonance imaging (MRI) studies can fill this gap by providing non-invasive measurements of the ageing brain's structure and function *in vivo* (Fjell and Walhovd, 2010). We next provide a brief introduction to this research technique, summarize the latest findings on

age-related brain changes and demonstrate how MRI may be used to reveal important insights into the underpinnings of leisure activity-cognition associations.

Table 1.1 A review of systematic reviews included on the association between cognitive activities, cognitive function and dementia risk. Reprinted from Matyas et al. (2019).

Reference	Aim	Search strategy	Included studies (N)	Study design	Total number of participants	Population	Outcomes	Risk of bias
Di Marco et al. (2014)	To provide a comprehensive summary of modifiable lifestyle factors (dietary habits, leisure activities, social network and so on) associated with the risk of late-onset incident dementia.	NR to 2013. PubMed, Ovid MEDLINE, PsycINFO, In-Process & Other Non-Indexed Citations. Search terms provided. English-language publications.	6 (cognitive leisure activities).	Longitudinal observational cohort studies.	NR	≥65 years, adults without dementia at baseline.	No quantitative analysis. Cognitive leisure activities might be associated with reduced incidence of all-cause dementia.	High
Opdebeeck et al. (2016)	To assess the relationship between cognitive reserve (educational level, occupational status and engagement in cognitively stimulating activities) and cognition in multiple domains.	NR to 2014. PubMed, PsycINFO, ScienceDirect, CINAHL. Search terms provided.	31 (cognitively stimulating activities).	31 cross-sectional studies.	24, 561	≥60 years (at least 80% of study participants).	SMD: 0.26 (95% CI 0.21 to 0.32). Participating in cognitive leisure activities is associated with *improved cognitive functions* (including memory, working memory, executive function, visuospatial ability and language).	High
Sajeev et al. (2016)	To assess if engaging in late-life cognitive activities is able to delay or prevent dementia.	NR to June 2014. PubMed and EMBASE. No search terms provided.	12 (cognitively stimulating activities).	10 prospective cohort studies; 2 nested case–control studies.	13, 939 (dementia: 1663; AD: 565)	≥45 years.	No quantitative analysis. Late-life cognitive activity might be associated with lower AD and/or all-cause dementia incidence.	Medium

Toril et al. (2014)	To investigate the extent to which cognitive training with video games enhances cognitive functions in healthy older adults.	1986–2013. MEDLINE, PsycINFO and Google Scholar. Search terms provided. English-language publications.	20 (video game training).	18 controlled studies; 2 uncontrolled studies.	913 (474 trained, 439 healthy controls)	50–86 years, healthy older adults.	SMD: 0.37 (95% CI 0.26 to 0.48). Video game training is associated with improved cognitive functions in older adults (including memory, attention, reaction time, cognitive function and executive functions).	High
Yates et al. (2016)	To assess the impact of cognitively stimulating leisure activities on cognition and risk of dementia in later life.	2004–2014. PsycINFO, MEDLINE, CINAHL, EMBASE and the Web of Science. Search terms provided.	19 (cognitive leisure activities).	17 cohort studies; 2 case–control studies.	32, 546	≥46 years, cognitively healthy adults (i.e, no diagnosis of impairment or dementia).	*All-cause dementia incidence:* RR: 0.61 (95% CI 0.42 to 0.90), k=3, RE.HR: 0.58 (95% CI 0.46 to 0.74), k=2, RE. OR: 0.78 (95% CI 0.67 to 0.90), k=2, FE. *Cognitive impairment incidence:* OR: 0.69 (95% CI 0.56 to 0.85), k=5, RE. HR: 0.85 (95% CI 0.71 to 1.02), k=3, RE, NS.	Medium

AD, Alzheimer's-type dementia; CINAHL, Cumulative Index to Nursing and Allied Health Literature; FE, fixed effects model; k, studies that assessed cognitive activities only; HR, Hazard Ratio; NR, not reported; NS, not significant; RE, random effects model; RR, risk ratio; SMD, standardised mean difference.

Table 1.2 A review of recent systematic reviews on the association between social activities, cognitive function and dementia risk.

Reference	Aim	Search strategy	Included studies (N)	Study design	Total number of participants	Population	Outcomes
Evans et al. (2018)	To conduct a systematic review and meta-analysis assessing the relationship between social isolation and cognitive function in later life.	NR to October 2016. PsycInfo, CINAHL, PubMed, and AgeLine. English language publications. Search terms provided.	39 (social activities).	Longitudinal observational cohort studies.	77, 954	≥ 50 years and with no cognitive impairment.	Higher levels of social activity was significantly associated with better global cognition (r = 0.072; 95% CI = 0.048 – 0.095). Domain-specific associations were also observed with memory (r = 0.049; 95% CI = 0.023 – 0.075) and executive function (r = 0.032; 95% CI = 0.011 – 0.052).
Kuiper et al. (2016)	To assess the relationship between poor social relationships and the development of cognitive decline in the general population, considering both structural (e.g. social network size) and functional elements of social relationships.	NR to July 2012. Databases were MEDLINE, Embase and PsycINFO. English; Dutch; German or French language studies were included. Search terms provided.	18 (social activities)	Longitudinal observational cohort studies.	25,791	NR although the samples of included studies were ≥ 50 years.	Lower levels of social activities linked to a higher risk of cognitive decline (OR: 1.08 (95% CI: 1.04-1.11)).
Kuiper et al. (2015)	To investigate the association between indices of social relationships (e.g. social isolation, social activity, loneliness) and incident dementia in the general population.	NR to July 2012. MEDLINE, Embase and PsycINFO. English; Dutch; German or French language studies were included. Search terms provided.	6 (social activities).	Longitudinal observational cohort studies.	7,714	NR although the samples of included studies were ≥ 55 years.	RE used. Lower levels of social activity participation was related to a higher risk of developing dementia, relative to individuals with higher levels of social activity (RR: 1.41 (95% CI: 1.13–1.75)).

Wang et al. (2012)	To examine the relationship between leisure activities, cognitive function and dementia.	1991 to March 2011. MEDLINE, MEDLINE plus, and PubMed were the selected databased used. English language publication. Search terms provided.	11 (social activities/social engagement)	Longitudinal and cross-sectional observational cohort studies.	17, 438	NR although the samples of included studies were ≥ 55 years.	No quantitative analysis conducted. *Risk of dementia:* two studies support a link, one study suggested no link, and one study highlighted late life but not mid life social engagement as a significant predictor. *Risk of incident cognitive impairment*: Results are inconclusive. Three studies reported positive effects, whereas three studies reported NS findings. *Cognitive function:* Mixed findings on whether social activities are linked to domain specific cognition.

Abbreviations- CINAHL = Cumulative Index to Nursing and Allied Health Literature; NR = not reported; NS = not significant; RE = random effects model; RR = risk ratio.

1.3 Principles of Magnetic Resonance Imaging

MRI is an informative, non-invasive technique that has begun to shed light on how the brain changes as a consequence of ageing (Fjell and Walhovd, 2010). A testament to its flexibility, MRI produces a range of images that provide insight into the different characteristics of the brain (i.e. *modalities*), including grey matter (GM) structure, the microstructural environment of white matter tracts and functional connectivity between brain regions (Jenkinson and Chappell, 2018). The following section serves as a brief introduction to MRI as a method used in this thesis, based on the detailed description found in Jenkinson and Chappell (2018).

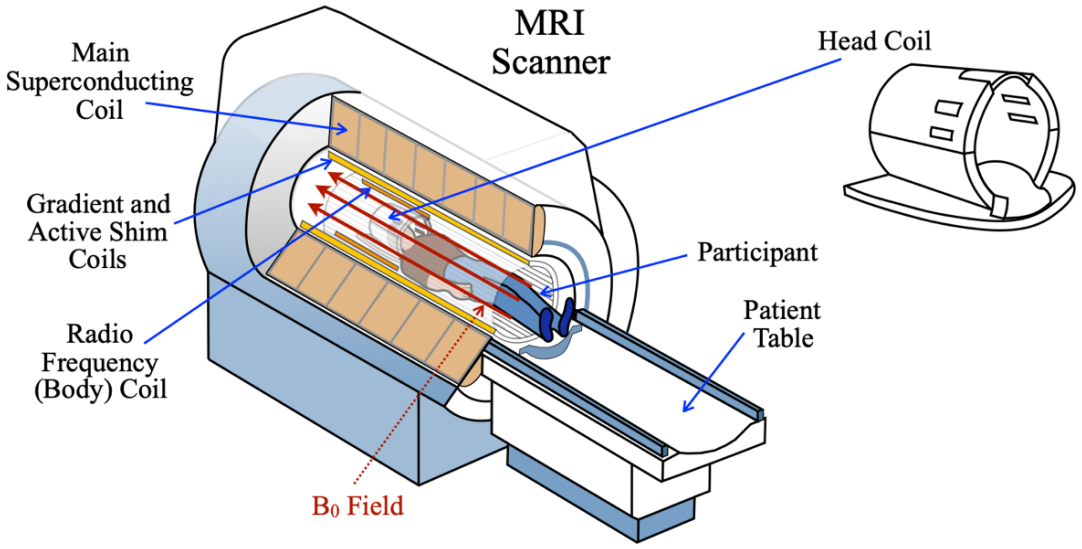
The images produced by MRI are made possible by its ability to detect and manipulate the magnetic fields of protons (i.e. hydrogen nuclei) attached to water molecules, which are abundant across different neural tissues. First, a continuously superconducting coil is used to produce the main magnetic field (i.e. B0 field, Figure 1.1), which represents the core field strength of any MRI scanner (e.g. 3T, 7T). The main purpose of the B0 field is to ensure that all protons within the scanned individual's brain are aligned with a single direction, as their otherwise random orientations make it impossible for a global signal to be detected. These protons are not static, but rather, continuously rotating around an axis, generating their own magnetic field. When they are aligned to the B0 field and are rotating in relation to its axis, their magnetic fields remain undetectable by the scanner. An essential stage to acquiring a measurable signal, is therefore to 'flip' the protons into the perpendicular or transverse plane.

Radiofrequency coils (Figure 1.1) embedded in the scanner take on the function of rotating these protons, by exploiting the fact that the rate at which a proton rotates (i.e. *resonance frequencies*) is proportional to the strength of an externally applied magnetic field.

Specifically, these coils create magnetic fields that 'tune into' the resonance frequencies of protons allowing them to manipulate the direction of protons. The resulting signal can then be picked up by radiofrequency receiver coils, including coils within a 'helmet' securely placed on the participant prior to scanning (i.e. head coil). The MRI signal represents a sum of all protons within the scanner although it is not immediately clear where different elements of the signal are localized to (e.g. within the brain). Gradients (Figure 1.1) are the third type of coils essential for developing MRI images, as they can be used to break down the global signal into localized sub-signals. These coils apply magnetic fields that *vary in strength* across the spatial extent of the scanner during data acquisition, causing resonance frequencies along the length of the gradient field to vary in a predictable manner. Given this mapping between resonance frequency and location, this information can be decomposed and used to reconstruct a three-dimensional image of the brain.

As the behaviour of protons is contingent on the type of tissue it is surrounded by (e.g. grey matter versus white matter), exploiting this phenomenon enables MRI to collect a variety of images that index separate aspects of the brain's morphology and function. In the subsequent sections, the key MRI imaging modalities are described in further detail, alongside the main insights that corresponding neuroimaging studies have provided into brain ageing.

Figure 1.1 Overview of MRI scanner hardware. Figure reprinted with permission from Jenkinson and Chappell (2018). © Oxford University Press.



1.3.1 MRI Measures of Grey Matter

T_1-weighted images are the most frequently collected modality in neuroimaging studies. These images are often the best quality from the set of modalities acquired and are particularly insightful into the macro-structural properties of the brain. For instance, a visual inspection of a T_1-weighted image reveals relatively good delineation of the brain's GM, white matter (WM) and cerebrospinal fluid (CSF). While the raw format of these images renders them unsuitable for statistical analysis, these images can undergo a series of processing steps that involve manipulating the images in order to allow for quantitative methods to be applied. A number of pre-processing pipelines are now available to aid in the analysis of neuroimaging data (e.g FSL Software library: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki; Freesurfer: https://surfer.nmr.mgh.harvard.edu/). These pipelines tend to converge in their pre-processing steps of T_1-weighted images, which include corrections for bias field and removing voxels containing non-brain material (i.e. brain extraction). There are then two main strategies to analysing these pre-processed

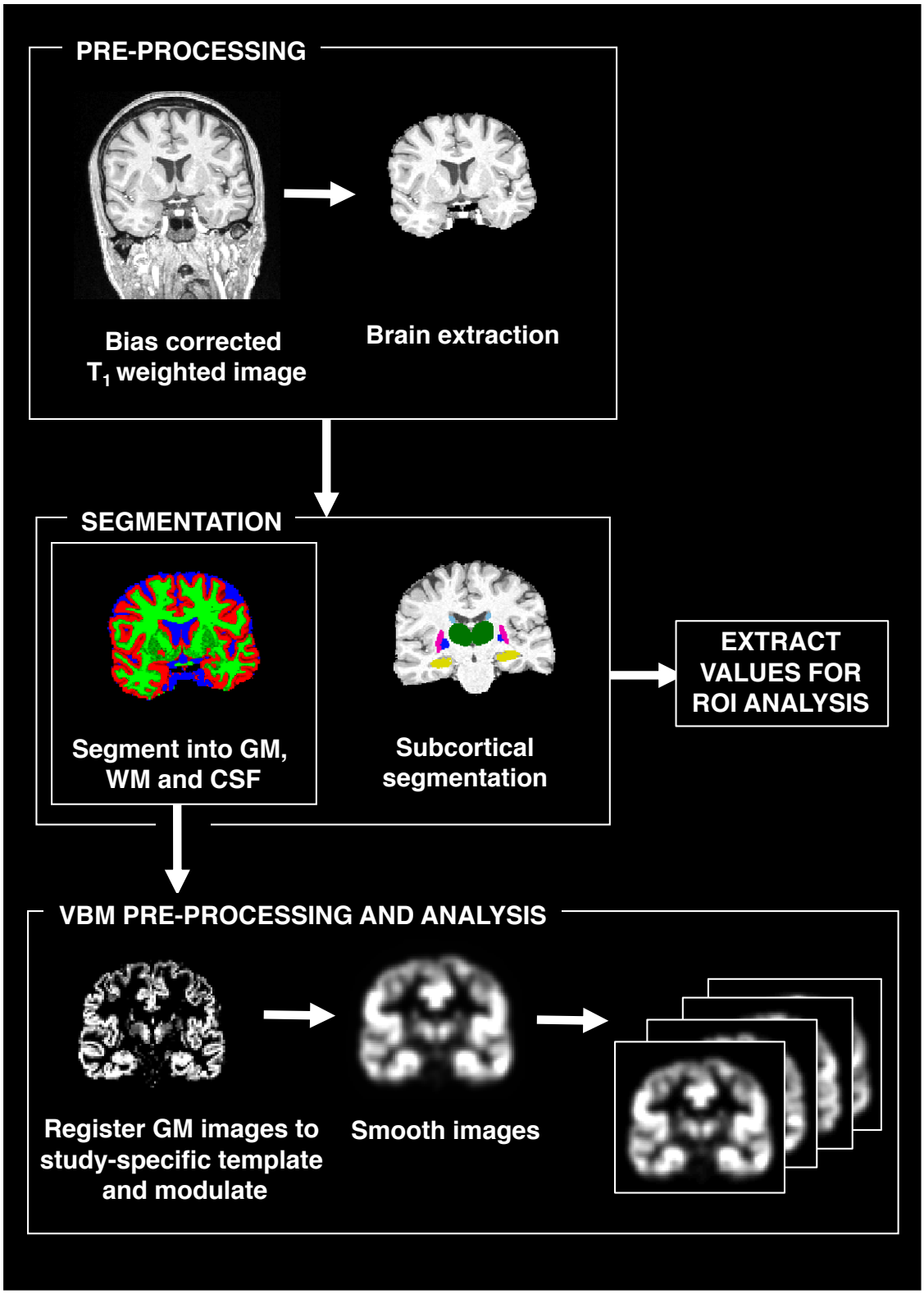
images: voxel-based morphometry (VBM) or region-of-interest (ROI) analyses, with an example of a pre-processing and analysis pipeline, available in Figure 1.2.

VBM is a type of analysis of GM that involves segmenting T_1-weighted images into GM, WM and CSF, then registering the GM segmented images of all participants to a standard space in order to compare, for example, differences in *regional* GM between a patient and healthy control group (Mechelli et al., 2005). The method has been widely used and is particularly advantageous due to its *hypothesis-free* exploratory nature, with the statistical tests conducted separately across every voxel containing GM tissue (i.e. mass 'univariate' tests; Whitwell, 2009). The main goal of this approach is to identify whether there are *clusters* (i.e. multiple neighbouring voxels) of GM that may reflect volumetric differences between groups. This approach is not without its limitations, given that it is particularly sensitive to errors in pre-processing, such as mis-registrations to standard space and the level of smoothing applied (Mechelli et al., 2005). Further, VBM can prove to be challenging for researchers without a background in MRI analysis.

An alternative method to VBM is ROI analysis (Sexton et al., 2013), which avoids issues related to spatial registration by parcellating the GM segmented T_1-weighted images into cortical and subcortical GM, all in subject-specific space (Jenkinson and Chappell, 2018). This method is also advantageous as the outcome is often a single numerical index to reflect a given brain region (e.g. hippocampal volume) and allows this information to be accessible to a wider range of researchers, without a pre-requisite for expertise in neuroimaging. The comparable simplicity and interpretability of ROIs may be one of the reasons for why MRI data from 'big data' studies are often available to external researchers in the form of image derived phenotypes (IDPs; e.g. UK Biobank; Alfaro-Almagro et al., 2018). It should be emphasized, however, that the *precision* of segmentation is key, as this

will determine whether the extracted number possesses any biological meaning (Hurtz et al., 2019). Although manual delineation or corrections to an automated output can substantially improve segmentation precision (Morey et al., 2009), this time-consuming task may not always be feasible in a sample exceeding several hundred individuals. The algorithms used to perform automated cortical and subcortical segmentation are, however, continually being revised and updated, with each new release striving to improve upon the shortcomings of the previous version.

Figure 1.2 Steps involved in the pre-processing of T1-weighted images for ROI and VBM analyses. Demonstrated using a single subject from the Whitehall II study, with the FSL pre-processing pipeline.



1.3.2 MRI insights into the Ageing Grey Matter

One of the hallmarks of ageing is GM atrophy. GM density tends to show increases between childhood and adolescence (Gennatas et al., 2017) after which it follows a general pattern of decline (e.g. Driscoll et al., 2009; Ge et al., 2002). Not all brain regions are equally affected by age, with age-related GM loss thought to proceed in an anterior-to-posterior pattern (Raz and Rodrigue, 2006). It is now well established that the frontal lobe is the most age-sensitive, with the occipital lobes least affected (e.g Allen et al., 2005; Fjell and Walhovd, 2010; Lemaitre et al., 2012; Raz et al., 2005). Age-related GM loss within the frontal lobes is estimated to occur at a yearly rate of 0.9 – 1.5% (Cabeza and Dennis, 2012). As a key structure implicated in AD pathology, it should come as no surprise that the hippocampus has received a lot of research attention over the years (e.g. Apostolova et al., 2012). The majority of findings are in agreement with the notion that this region shrinks with age, although they also highlight other subcortical areas to correlate with age (e.g. putamen, amygdala; Fjell and Walhovd, 2010). Annual rates of decline in hippocampal volume are estimated to be between 0.8% - 2.0%, but these estimates are likely confounded by the curvilinear pattern of hippocampal change emerging from longitudinal MRI findings (Fjell and Walhovd, 2010). The proposed anterior-posterior gradient of GM loss and hippocampal atrophy may go some way in explaining declines in executive functions (Cabeza and Dennis, 2012) and episodic memory (Bird and Burgess, 2008), respectively. Recent findings provide backing for this hypothesis, for example, by consistently demonstrating that age-related impairments to executive function performance are directly linked to reductions in GM volume in the frontal lobe (Kievit et al., 2014; Manard et al., 2016).

Although it is not possible to determine the specific molecular and cellular processes *driving* the age-related GM changes with MRI alone, neuropathological studies of the brain and

animal studies have long been used to supplement our understanding of neural ageing. Historically, differences in post-mortem brain weight between young and old individuals (e.g. Dekaban and Sadowsky, 1978) and early rodent studies conducted between the 1950s-70s (reviewed in Hanley, 1974) worryingly suggested the brain exhibits "neuronal fall-out" i.e. widespread neuronal death. These early findings have not, however, held the test of time, as improvements in the methods used to quantify neurons and essential adjustments for age-related atrophy suggested that only between 2-4% of cortical neurons are lost over the lifespan (von Bartheld, 2018). Other explanations have since been put forward, including reductions in neuronal size, loss in synaptic density and dendritic spines (Dickstein et al., 2013; Peters, 2006). As age-related brain changes are not restricted to GM tissue and have also been observed for the connecting WM tracts (Peters, 2006), the next section begins by describing an MRI modality sensitive to the microstructural environment of WM, followed by a review of insights that this method has provided into the ageing WM.

1.3.4 MRI Measures of White Matter

Diffusion tensor imaging (DTI) is a MRI modality that provides more detailed insight into the microstructural properties of WM tracts, compared to the macrostructural measures of WM acquired through T_1-weighted images (Madden et al., 2012; Soares et al., 2013). This modality is sensitive to the diffusion of water molecules, which moves in a directional-dependent manner in and around WM tracts (*anisotropic* diffusion) while diffusing at the same rate in all directions in other tissue types i.e. CSF (i.e. *isotrophic* diffusion; Soares et al., 2013). The directional preference is mainly attributed to restrictions in movement imposed by the presence of WM fibres in the environment (e.g. cellular membranes, myelin sheaths) through which water molecules cannot easily diffuse. In and around healthy axonal bundles, water molecules will be restricted to largely diffuse in a direction parallel to the

tracts within both an intra-cellular and extra-cellular environment (Jenkinson and Chappell, 2018). In the presence of necrosis or demyelination, for instance, the rate of diffusion in all directions would conversely be expected to increase (Alexander et al., 2007). Gradients are the key to acquiring diffusion-weighted images, with water molecules diffusing along the gradients causing signal attenuation (Jenkinson and Chappell, 2018). Notably, signal attenuation is proportional to the magnitude of diffusion. To clarify the nature of water diffusion (e.g. rate, direction), many different gradient directions need to be acquired (at least minimum of 6 directions; Alexander et al., 2007). These signal attenuations measured in different directions can then be used to compute the amount of diffusion of underlying water molecules, from which inferences about the WM's microenvironment are drawn (For a detailed description of diffusion-weighted imaging, please see Soares et al., 2013).

In order to derive indices that are sensitive to the structural features of WM tracts, a diffusion tensor model is applied to every voxel during the early stages of processing diffusion-weighted images. Several mathematical models are now available (e.g. Neurite Orientation Dispersion and Density Imaging; NODDI; Zhang et al., 2012), with diffusion tensor model the most widely adopted. Anisotropic diffusion is modelled as an ellipsoid within voxels containing WM fibres (see Figure 1.3), with its longest axis corresponding to the principal direction of diffusion within a given voxel (Soares et al., 2013). When a voxel contains CSF or GM, the tensor model will instead take on the form akin to a flattened sphere (or 'pancake' shape) to reflect isotropic diffusion (Jenkinson and Chappell, 2018). The diffusion tensor is able to provide several metrics describing the behaviour of water molecules, most commonly, fractional anisotropy (FA), mean diffusivity (MD) axial diffusivity (AD) and radial diffusivity (RD), which are each described in Table 1.3. At no point, however, do these metrics have a one-to-one mapping with a specific biological phenomenon (O'Donnell and Pasternak, 2015; O'Donnell and Westin, 2011). For

example, changes in FA may indicate a number of events, including cell death, inflammation, myelination changes and gliosis (O'Donnell and Pasternak, 2015). Non-specificity of diffusion metrics is not the only drawback of the diffusion tensor model, which also performs poorly in voxels containing crossing fibres and may be imprecise in voxels containing two tissue types (O'Donnell and Westin, 2011). Alternatives to the diffusion tensor model (e.g. NODDI) and advances in data acquisition (High angular resolution diffusion imaging; Tuch, 2004), have been proposed to address these constraints of the tensor model.

DTI measures (e.g. FA) can be examined as correlates of behaviour or otherwise compared between groups (e.g. young and old). Depending on the research question, several methods can be used to test these correlations or group differences, including (1) whole-brain voxel-wise approaches (e.g. tract based spatial statistics (TBSS); voxel-based analysis (VBA)), (2) ROI analyses or (3) tractography (Wassenaar et al., 2019). As seen for T_1-weighted images, diffusion weighted images are required to undergo a series of processing steps (e.g. corrections for head motion, eddy currents, brain extraction and diffusion tensor fitting) prior to quantitative analysis (Jenkinson and Chappell, 2018). In the case of TBSS, a sample-specific FA tract skeleton is then produced, which is subsequently used to derive subject-specific FA tracts for voxel-wise statistics (Smith et al., 2006). TBSS is recommended over VBA, as the latter runs the risk of mis-registration and smoothing-related issues (Soares et al., 2013). TBSS is however, more sensitive to voxels based in the centre of tracts compared to voxels located along the tract edges (Mueller et al., 2015). If a researcher is interested in a particular tract, then a ROI-based analysis may instead be warranted. This would involve using a manual or atlas-based approach to segment the tract of interest (e.g. corpus callosum) in order to derive a summary measure of the region, such as mean FA (Wassenaar et al., 2019). Although this method bypasses any registration issues

experienced in VBA, it is insensitive to regional differences within a large structure such as the corpus callosum. With automated methods now available (e.g. PROBTRACKX**,** Behrens et al., 2007, 2003) tractography is the third type of analysis tool that a researcher can employ. Tractography fundamentally involves tracing the principal direction of diffusion within each voxel to produce a three-dimensional reconstruction of WM fibres (Soares et al., 2013). The accuracy of tracing is dependent on the mathematical model used to represent diffusion (e.g. the diffusion tensor will struggle with voxels containing crossing fibres), with this method also susceptible to producing false positive connections (Jbabdi et al., 2012; Maier-Hein et al., 2017).

Figure 1.3 Schematic diagram of the diffusion tensor model. In the presence of anisotropic diffusion (such as in and around healthy white matter fibres), the diffusion tensor model adopts an ellipsoid shape, with the longest axis (λ_1) reflecting the principal direction of diffusion. Based on Figure 1 from Johansen-Berg and Rushworth (2009).

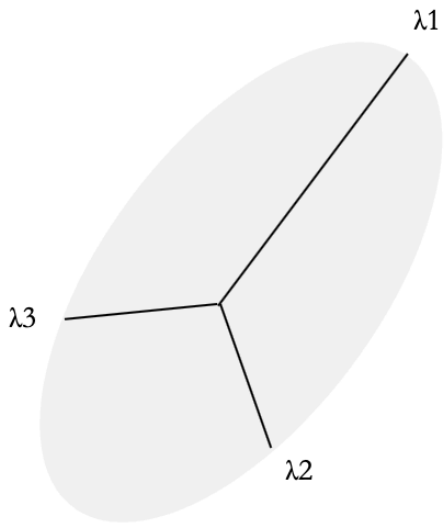


Table 1.3 Description of the metrics derived from the diffusion tensor model, as provided in Soares et al. (2013).

Metric	Calculation	Description
Fractional Anisotropy	$\sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{(\lambda_1^2+\lambda_2^2+\lambda_3^2)}}$	The directional preference of anisotropic diffusion. This value ranges between 0 (isotropic diffusion) to 1 (anisotropic diffusion).
Mean Diffusivity	$(\lambda_1+\lambda_2+\lambda_3)/3$	The average magnitude of diffusion, irrespective of direction. Higher values reflect increased diffusion.
Axial Diffusivity	λ_1	Diffusion rate parallel to the main axis of diffusion. Higher values index greater diffusion.
Radial Diffusivity	$(\lambda_2+\lambda_3)/2$	Diffusion rate perpendicular to the main axis of diffusion. Higher values indicate increased diffusion.

1.3.5 MRI Insights into the Ageing White Matter

Early volumetric studies have provided insight into the curvilinear pattern of change that WM follows over the lifespan: increasing until the second decade of life, and then remaining relatively stable before declining in the sixth decade of life (Raz, 2004). Both cross-sectional and longitudinal DTI studies have largely produced complementary findings, suggesting that ageing in the later stages of life correlates with reduced integrity of WM tracts, as indicated by reductions in FA and increases in MD and RD (Bender and Raz, 2015; Bennett and Madden, 2014; Cox et al., 2016). Findings are, however, mixed for another DTI metric, AD (Bennett and Madden, 2014). Neuropathological investigations additionally indicate that the WM changes detected by MRI may be driven by a number of microstructural events, including malforming, splitting, or degenerating myelin, and axonal injury (Gunning-Dixon et al., 2009; Madden et al., 2012). At a regional level, the patterns of decline across tracts have been widely reported to occur in an anterior-to-posterior direction (Bennett and Madden, 2014; Cox et al., 2016), giving rise to the notion that late myelinating tracts may be the most vulnerable to ageing (Bartzokis, 2004; Brickman et al., 2012; Reisberg et al., 1999). Notably, other vulnerability patterns have since emerged in the literature, such as an inferior-to-superior gradient (Sexton et al., 2014).

T_2 Fluid-attenuated inversion recovery (FLAIR) imaging has further contributed to our understanding of the ageing brain, by demonstrating that WM lesions or *hyperintensities* are present even among asymptomatic older adults (de Leeuw et al., 2001; Wen and Sachdev, 2004). Estimates of the prevalence of periventricular WM hyperintensities have ranged between 39-96% of the older adult population (Prins and Scheltens, 2015) with anterior regions particularly affected (Habes et al., 2016). The exact cause of WM lesions may vary, including long-term ischemia due to small vessel disease, myelin and axonal loss (Sachdev et al., 2007). The quality and quantity of WM lesions can be probed by using manual visual

rating scales (Scheltens et al., 1993) or automated segmentation programs, respectively (Griffanti et al., 2016). Overall, the onset of WM lesions and reductions in WM quality have been repeatedly linked to cognitive decline in older adults, emphasizing that targeting these age-related brain changes may have important consequences for cognitive health (Bennett and Madden, 2014; Gunning-Dixon et al., 2009; Habes et al., 2016; Prins and Scheltens, 2015).

1.3.6 MRI Measures of Functional Connectivity

In our discussion so far of structural imaging modalities, we have demonstrated that these methods have made critical advances in our understanding of the brain's morphology as it ages. However, focusing exclusively on structural markers overlooks the fact that the brain is a dynamic organ with its *activity* ultimately giving rise to cognitive function. This is where functional MRI (fMRI) is useful, as it provides *in vivo* assessments of regional brain activity as it occurs, under different experimental conditions (Bijsterbosch et al., 2017). Before delving into the details of fMRI, it is important to clarify that this method cannot provide a direct measure of neuronal activity, but rather, is only sensitive to the *hemodynamic response* to neural activity (Ferreira and Busatto, 2013). Alternative techniques exist that are able to detect the average electrical impulse omitted by cortical neurons (i.e. electroencephalography (EEG), Constant and Sabourdin, 2012), although the drawback of these methods is that they are often unable to precisely localize the signal received (Michel and Brunet, 2019). fMRI, on the other hand, possesses good spatial resolution (Fox and Raichle, 2007). It also represents a less invasive method than compared to other functional assessments of the brain (e.g. Positron Emission Tomography (PET); Mevel et al., 2011).

fMRI is particularly receptive to haemoglobin, which exists in both an oxygenated and deoxygenated state with different magnetic properties (Ferreira and Busatto, 2013). When

neurons within a region become active, the surrounding vessels dilate to supply more blood (i.e. Cerebral Blood Flow (CBF)) leading to an oversupply of oxygenated blood that causes a depletion in the concentration of deoxygenated haemoglobin in vessels proximal to the region of heightened neuronal activity (Glover, 2011; Jenkinson and Chappell, 2018). The MRI scanner is most sensitive to deoxygenated haemoglobin, which causes local magnetic field disturbances that weaken the overall MRI signal. When a brain region's activity triggers an increase in CBF, raising the concentration of oxygenated relative to deoxygenated haemoglobin, the corresponding MRI signal becomes *stronger* compared to its baseline (Jenkinson and Chappell, 2018). These regional changes in oxygenated blood concentration over time are otherwise known as the BOLD (i.e. Blood Oxygen Level Dependent) response, with the resulting images referred to as T2*-weighted images (Ferreira and Busatto, 2013). Unfortunately, the BOLD response is not tightly coupled to neuronal activity, with its peak occurring approximately 5-6 seconds after the onset of neural (Jenkinson and Chappell, 2018). Despite this shortcoming, fMRI has nevertheless provided a window into the activity of the brain and its functional architecture.

As the terms allude, task and resting-state fMRI are conducted under different conditions. During task fMRI, the participant is required to perform a pre-defined task (e.g. cognitive, sensory or motor) with the aim of identifying areas of increased/decreased activation during task performance (Glover, 2011). Resting-state fMRI on the other hand does not necessitate task participation, instead requiring participant to remain still (and awake) in the scanner without thinking about anything in particular (Bijsterbosch et al., 2017). In the latter type of data acquisition, the goal is to examine whether low-level fluctuations in the BOLD response (i.e. < 0.1 Hz; Fox and Raichle, 2007) of different brain regions correlate, over time (Sala-Llonch et al., 2015). Although resting-state fMRI was initially met with fierce scepticism from the scientific community (Snyder and Raichle, 2012), it is now a

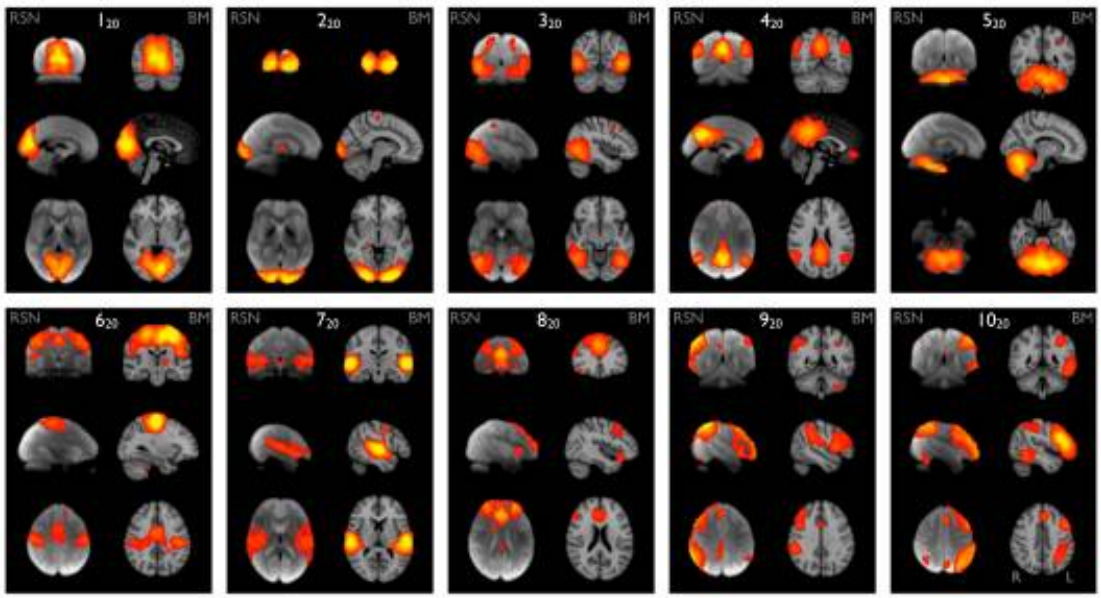
widely accepted as a fundamental approach to examining the brain's functional organization and has also been recognized to possess certain advantages over task fMRI. For example, given the minimal demands placed on participants during resting-state fMRI, it allows for a wider variety of individuals to be assessed, including children, older adults and dementia patients (Bijsterbosch et al., 2017). Furthermore, it also provides better signal-to-noise (as it discards less of the data) and explains a greater amount of the variance (50-80%) in the BOLD signal then compared to conventional task-based (20%) approaches (Fox and Greicius, 2010). The results of resting-state fMRI are also less confounded by factors including task performance, group differences in effort or energy (for example between young and old adults) and longitudinal investigations are less vulnerable to practice effects often seen in task-based paradigms (Fox and Greicius, 2010). Given these advantages, we focus the rest of our discussion predominately on resting-state fMRI.

As the fast-paced methods used to acquire T2* images (i.e. echo-planar imaging) can lead to motion artefacts and image distortion (Jenkinson and Chappell, 2018), these images necessitate a number of pre-processing steps before the analysis stage. These steps include, but are not limited to motion correction, field map corrections, high pass temporal filtering and standard space registration (Bijsterbosch et al., 2017). There are then several ways to analyse these images. One method is the ROI based approach, which involves examining temporal correlations in the BOLD timeseries (i.e. functional connectivity) between a pair or multiple *a priori* defined brain regions (Rosazza et al., 2012). The connectivity of a single seed can also be mapped to the rest of the brain in a voxel-wise manner (i.e. seed based analysis; Fox and Raichle, 2007; Rosazza et al., 2012). Importantly, the same seed is often applied across all participants meaning that inter-individual differences in the extent of a given region are unaccounted for, and the method used to define ROIs can affect the

accuracy of functional connectivity estimates (Sohn et al., 2015). Another no less important point is that there may not always be sufficient evidence for a researcher to identify brain regions of interest in advance of their study.

A whole-brain, hypothesis-free approach is alternatively available and is presently widely employed, known as Independent Component Analysis (ICA). ICA is based on algorithms designed to extract group-level spatial maps of independent components that account for the variance in BOLD response (Bijsterbosch et al., 2017). This method has revealed the existence of large-scale functional brain networks including visual, auditory, sensorimotor, default mode and executive control networks (Beckmann et al., 2009, 2005; Fox et al., 2005), which can be compared across groups (e.g. between young and older individuals). Strikingly, ICA-derived networks are highly replicable across studies and sessions with good test re-test reliability (Damoiseaux et al., 2006) and demonstrate correspondence with task-based activation (Smith et al., 2009). An added advantage of ICA is that it also provides a powerful data denoising technique (Griffanti et al., 2014). The disadvantages of this approach is that it is not always clear as to whether a component reflects structured noise, signal or a mix between the two and the outcome is often determined by the number of components that the user specifies to ICA to extract, which can vary between studies (Fox and Raichle, 2007; Rosazza et al., 2012). Graph theory is a third analysis approach that involves modelling the brain as a complex network to derive estimates of its the functional organization and connectivity (van den Heuvel and Hulshoff Pol, 2010; Wang et al., 2010). The disadvantages of this method is that it is often based on full correlations between different nodes introducing confounds into the metrics, with these metrics often difficult to map on to underlying functional processes (Bijsterbosch et al., 2017).

Figure 1.4 Example of large-scale resting-state networks identified using ICA. Pairs of networks derived from a 20-component ICA in a study of 36 participants (networks on the left-hand side of each panel) and separately on a dataset of 29,671 participants (BrainMap activation database; networks on the right of each panel). All networks are overlaid on a MNI152 standard space template. Reproduced with permission from Smith et al. (2009). Copyright (2009) National Academy of Sciences.



Labels according to original publication: Component 1_{20} = Medial Visual Network; Component 2_{20}= Occipital Visual Network; Component 3_{20}= Lateral Visual Network; Component 4_{20} = Default Mode Network; Component 5_{20} = Cerebellar Network; Component 6_{20} = Sensorimotor Network; Component 6_{20} = Sensorimotor Network; Component 7_{20} = Auditory Network; Component 8_{20} = Executive Control Network; Component 9_{20}-10_{20} = Frontoparietal Network.

1.3.7 MRI Insights into Functional Connectivity and Ageing

While early fMRI investigations of health ageing have mainly adopted task-based paradigms, there has been a heavy uptake of resting-state fMRI in more recent years (Hafkemeijer et al., 2012). Among the large-scale resting-state networks identified through ICA (Beckmann et al., 2005), the Default Mode Network (DMN) is the most extensively studied in part due to its sensitivity to Alzheimer's disease (Dennis and Thompson, 2014; Sorg et al., 2009). The DMN is considered a 'task negative' network (i.e. activation increases at baseline when compared to task performance) and is linked to a number of cognitive processes such as planning, recalling memories, appraising thoughts and perspectives of others (Andrews-hanna et al., 2009; Reineberg et al., 2018). Several key

structures give rise to this network, including the medial prefrontal cortex, posterior cingulate cortex/precuneus, inferior parietal lobe and hippocampal formation (Buckner et al., 2008). DMN intra-network connectivity follows a curvilinear trajectory across the lifespan (Mak et al., 2017; Staffaroni et al., 2018), with a recent meta-analysis of voxel-wise studies demonstrating that DMN connectivity increases in childhood and is then followed by an attenuation between early to mid/late-adulthood (Mak et al., 2017). Studies using ICA have established a relationship between age-related changes in the DMN and declines in cognitive performance, including autobiographical (Mevel et al., 2013) and episodic memory (Persson et al., 2014).

As seen earlier in our discussion, executive function or cognitive control abilities tend to decline with age. Several networks have been implicated in maintaining these higher-level cognitive abilities, including the Executive Control Network (ECN) and the Fronto-parietal Network (FPN; Petersen and Posner, 2012). The ECN crucially involves the anterior cingulate cortex, frontal pole, paracingulate gyrus and inferior and middle frontal gyri, among other regions and is implicated in directing and focusing attention during cognitively demanding tasks (Beckmann et al., 2005; Smith et al., 2009; Trachtenberg et al., 2012). The FPN (also a 'task positive' network as the ECN; Seeley et al., 2007; Turner and Spreng, 2015) is instead suggested to play a role in modifying behaviours in response to task demands (Marek and Dosenbach, 2018; Petersen and Posner, 2012). This network (also known as the 'dorsal visual stream', Vincent et al., 2008) is the most consistent to show lateralization with ICA-based approaches, with some findings suggesting dissociable cognitive functions (Smith et al., 2009). The right FPN includes the right middle and superior frontal gyrus, right inferior parietal cortex, right occipital cortex, and bilateral intraparietal sulcus (Beckmann et al., 2005). The left FPN mirrors the pattern of regions in the left hemisphere, also integrating the bilateral intraparietal sulci. The ECN and FPN

are frequently observed to negatively correlate (i.e. *anti-correlate*) with the DMN, suggesting that the activation of one network coincides with the suppression of another (Chan et al., 2014; Fox et al., 2005; Wig, 2017). Age appears to not only reduce intra-network connectivity of these networks but also render the connectivity between networks more positive (i.e. age *attenuates* anti-correlations; Benson et al., 2018; Ferreira et al., 2016; Spreng et al., 2016), leading to the hypothesis that networks become less segregated in late life (Ng et al., 2016). Given the implications that these functional connectivity changes may have for cognitive function, resting-state network connectivity is a potential endpoint when considering the effects of a modifiable factor, such as leisure activities, on the ageing brain.

1.4 Plasticity in the ageing brain

MRI has been central to advancing our understanding on how the brain changes with age, potentially underlying the observable declines in cognitive performance during late life. Yet in the same way that cognitive function is malleable to experience, neuroimaging findings are accumulating to suggest that, so too, is the brain (Chan et al., 2014; Ng et al., 2016; Turner and Spreng, 2015). One of the earliest and most well-known MRI investigations to probe experience-dependent changes in brain structure (i.e. brain plasticity) was a study by Maguire and colleagues (2000), who found that London taxi drivers exhibited greater GM volume in the posterior hippocampi than controls, and GM in this region correlated positively with taxi driving experience. Since its publication, the number of studies demonstrating GM modifications after learning or practicing a learned skill has grown rapidly, including musical training (Schneider et al., 2002), juggling (Draganski et al., 2004; Driemeyer et al., 2008), CT (Valkanova et al., 2014) and physical activity (Erickson et al., 2014). WM tracts also demonstrate training-dependent alterations, usually indexed by increases in FA and decreases in MD within functionally relevant tracts, although other patterns have also been reported (Sampaio-Baptista and Johansen-Berg,

2017). Resting state fMRI is additionally sensitive to rapid changes in plasticity, as demonstrated by changes in intra-network connectivity or coupling between regions or networks after various types of training (Guerra-Carrillo et al., 2014). For example, enhanced FPN and cerebellar network strength has been reported after a mere 11-minute session of visuomotor training (Albert et al., 2009). Overall, these widespread MRI changes may reflect a number of cellular processes, including neurogenesis, synaptogenesis, changes in axonal number or diameter, dendritic or axon branching (Zatorre et al., 2012), to name a few.

Notably, brain plasticity is not restricted to the early stages of life as once thought, with older adults also exhibiting experience-dependent structural and functional changes as observed in their younger counterparts (Holman and de Villers-Sidani, 2014). Given that our earlier review of epidemiological evidence identified cognitive and social activity levels as linked to better cognitive health among elderly adults, a core question that remains is whether these changes in cognitive function are also accompanied by underlying structural and functional adaptations, within this rapidly growing demographic.

1.5 Aims

The overarching aim of this thesis is to investigate whether cognitive and social activities relate to MRI markers of brain structure, functional connectivity and cognitive function in community dwelling older adults.

Only a handful of neuroimaging studies have examined how activities relate to underlying brain structure, without any systematic efforts to summarize these findings. Chapter 2 therefore conducted a systematic review and meta-analysis, with the aim of pooling

together available evidence to clarify the current state of knowledge on activity-brain associations.

Given the absence of previous studies known to have evaluated leisure activities in relation to resting-state functional connectivity, Chapter 3 investigates whether *late life* participation in cognitive and social activities relate to MRI measures of brain structure, functional connectivity and cognitive performance using data collected from the Whitehall II cohort.

As prior evidence suggests that leisure activity habits change between mid-life and late life (Pinto and Neri, 2017), Chapter 4 revisited the Whitehall II dataset with the aim of: a) delineating the pattern of cognitive and social activity changes over time and b) examining whether *activity trajectories* relate to brain structure, functional connectivity and cognition in late life.

Chapter 5 aimed to 'break down' the commonly used composite measures of cognitive activities, to identify whether there are particular activities that independently contribute to brain integrity in late life. To address this aim, data from the UK Biobank study was examined.

The subsequence chapters describe the rationale, methods and results of each project, with Chapter 6 providing a summary of these findings and a discussion of several core methodological themes to arise from this work, alongside suggestions for future work.

CHAPTER 2

A Systematic Review and Meta-Analysis on the Relationship Between Leisure Activities and Brain Structure in Healthy Older Adults

Contents

Abstract 49

2.1 Introduction 49

2.2 Methods 53

2.3 Results 58

2.4 Discussion 75

2.5 Conclusion 87

Abstract

As an individual gets older, their cognitive abilities can change – sometimes, for the worse. Yet emerging findings suggest that cognitive decline is not an inevitable consequence of ageing, and a mentally and socially enriched lifestyle may help promote cognitive function during the later years of life. The underlying neural mechanisms supporting the associations between socio-intellectual activities and cognition are, however, largely unknown. This chapter aims to summarize what is already known about the associations between cognitive and social activities and MRI measures of brain structure, including grey matter volume and white matter microstructure.

To address this chapter's research aim, a systematic search was conducted across several key databases (i.e. MEDLINE, PUBMED and EMBASE), in order to identify cross-sectional and longitudinal observational studies that had examined the relationship between cognitive and social activities and MRI markers of brain structure, among

community-dwelling older adults. A meta-analysis was also used to quantify the associations between activities and brain structure, where possible. From an initial 450 articles, 18 studies met the inclusion criteria of this review (total n = 8429). Our main finding was that, when combined, socio-intellectual activities were related to better global measures of white matter microstructure and regional grey matter volume, in addition to fewer lesions within the white matter tracts of the brain. The effect sizes, however, were notably small. Additionally, the extent to which activities correlated with the microstructural properties of white matter tracts could not be determined due to an insufficient amount of evidence.

Although the observational nature of the reviewed evidence precludes any decisions about the direction of the associations reported, the results described here offer the possibility that improving engagement levels in cognitive and social activities among healthy older adults could be an important avenue for supporting brain health into the later years of life. However, the review also highlights key methodological issues that if left unaddressed, could hinder progress in this field. This chapter offers suggestions to avoid common pitfalls and to ensure that future work contributes to better delineating the relationship between leisure activities and the brain.

The Chapter was published in *Neuroscience and Biobehavioural Reviews*, under the title "A systematic review and meta-analysis of structural magnetic resonance imaging studies investigating cognitive and social activity levels in older adults" (Anatürk et al. 2018).

Keywords: cognitive activity, social activity, grey matter, white matter, meta-analysis

2.1 Introduction

In response to the ageing of the general population, there has been considerable interest within the scientific community to establish whether leisure activities are protective determinants of cognitive ageing (Fratiglioni et al., 2004; Kuiper et al., 2016; Wang et al., 2012; Yates et al., 2016). Epidemiological studies in particular have yielded promising results, with one meta-analysis suggesting that cognitive activities are significantly correlated with a lower risk of cognitive decline and dementia, higher levels of global cognition and better performance on tests of executive functioning, memory, processing speed and language (Yates et al. 2016). Another meta-analysis found that infrequent participation in social activities is related to a faster rate of mental decline (Kuiper et al., 2016). While the link between leisure activities and late life cognition is now well established, the neurobiological mechanisms supporting these associations are not yet fully understood.

Neuroimaging techniques provide a powerful tool to examine the neural mechanisms underlying the link between leisure activities and old age cognition (Bartrés-Faz and Arenaza-Urquijo, 2011). Existing neuroimaging studies can be broadly divided into three categories: (1) structural MRI (2) fMRI and (3) Positron emission tomography (PET)/Single-photon emission computed tomography (SPECT) imaging. As described in the thesis introduction, structural MRI captures the neuroanatomical properties of the brain, including global and regional grey matter (GM) and white matter (WM) volume, WM microstructure and WM lesions (Giorgio et al., 2010). These structural features have been proposed as indices of *'brain reserve'* (Stern, 2002; 2012), where higher levels (e.g. greater GM and WM volume) correspond to a better tolerance of age- and disease-related damage (Bartrés-Faz and Arenaza-Urquijo, 2011; Katzman et al., 1988; Mortimer et al., 2003; Stern, 2002, 2012). In contrast, task-based and resting-state fMRI can investigate

activation patterns and functional connectivity (Gerchen and Kirsch, 2017). These approaches have been used to investigate mechanisms underlying *'cognitive reserve',* referring to the brain's functional capacity to adapt to - or compensate for - age- or disease-related neural insult (Bartrés-Faz and Arenaza-Urquijo, 2011; Stern, 2012). Finally, PET and SPECT studies are sensitive to several different biomarkers of Alzheimer's disease (AD) pathology, including beta amyloid deposition, hypometabolism and perfusion deficits (Scheltens et al., 2016). Leisure activities are widely considered to have *neuroprotective* effects on the ageing brain, either by (1) promoting *brain reserve*, (2) supporting *cognitive reserve*, or (3) disrupting the progression of Alzheimer's Disease (Arenaza-Urquijo et al., 2015; Stern, 2002, 2012). Given that the findings of PET and SPECT studies have been comprehensively summarized and discussed elsewhere (Arenaza-Urquijo et al., 2015), and fMRI studies are few in number, this review will primarily focus on structural MRI studies to evaluate the hypothesized role of leisure activities in *brain reserve*.

A growing number of studies using MRI techniques have begun to explore the relationship between leisure activities and brain structure in old age (e.g. Foubert-Samier et al., 2012; James et al., 2012; Valenzuela et al., 2008; Vemuri et al., 2016), with mixed evidence regarding whether cognitive activities consistently relates to structural MRI markers of ageing (Cheng, 2016). As we are not aware of any comprehensive systematic reviews or meta-analyses, we aim to address this gap in the present review.

2.1.1 Aims

Specifically, our main objective is to systematically summarize the results of cross-sectional and longitudinal MRI studies that have investigated whether levels of cognitive and social activities related to brain structure in older populations. While issues in defining the sub-types of leisure activities are later discussed, for the purposes of this review we use existing

definitions of cognitive and social activities. Cognitive activities refer to hobbies that predominantly require mental engagement with minimal interpersonal interactions, while social activities are those where the core feature is socializing with others (Seider et al., 2016). As age affects both GM and WM tissue (Raz and Rodrigue, 2006), we include structural and diffusion-weighted MRI markers in this chapter to gain insight into whether leisure activities relate to both macro- and micro-structural properties of the ageing brain. Based on the rationale that leisure activities are neuroprotective (Arenaza-Urquijo et al., 2015; Bartrés-Faz and Arenaza-Urquijo, 2011; Stern, 2012), we hypothesize that frequently participating in cognitive and social activities will be associated with greater GM and WM volume, higher WM integrity and fewer WM lesions.

2.2 Method

2.2.1 Data Sources

Studies were searched for on the online databases EMBASE, MEDLINE and PSYCHINFO, using the interface MEDLINE Ovid in December 2017. The list of terms used in the formal search strategy was compiled after conducting a preliminary exploration of existing literature, where the keywords of articles deemed to be potentially relevant were extracted. An example of the keywords used for the MEDLINE search are shown in Appendix 2.1. These terms were adapted for the two remaining databases. The reference lists of relevant studies were also screened to ensure that all literature appropriate to the review was captured and assessed for eligibility.

2.2.2 Inclusion Criteria

1. Published as a research article.
2. Participation in cognitive or social activities was directly assessed with a self-report questionnaire. To maximize the number of studies included in this review, those that

had measured both types of activities and combined them for the analyses to produce an overall score in leisure activity levels were also included.

3. The study included a single MRI session (cross-sectional design) or multiple MRI assessments (longitudinal design).
4. An observational study design was used. This criterion was introduced to ensure that the included studies were relatively homogenous in design, allowing for the results to be sufficiently comparable.
5. At least one of the following MRI measures was examined in the study: GM volume, WM volume, WM integrity (e.g. FA, MD) and the presence and severity of WM lesions.
6. The relationship between activity levels and MRI outcomes or group differences in MRI outcomes (i.e. between groups with high/low activity levels) was directly examined. Mediation analyses (e.g. examining whether measures of GM volume mediated the association between activity levels and cognitive function) were not included.
7. The sample consisted of healthy older adults (i.e. without a diagnosis of dementia) with a mean age 60 years or over.
8. The study was published in the English language.

2.2.3 Study Identification and Selection

Melis Anatürk (MA) and Naiara Demnitz (ND) independently screened the titles and abstracts of all of the citations identified by the search. These authors also reviewed the full text versions of a subset of citations to evaluate whether they met the eligibility criteria for inclusion.

2.2.4 Data Extraction

MA and ND separately carried out data extraction using identical structured forms, which were subsequently compared to ensure consistency and accuracy in the information collected. The study-specific information collected included sample characteristics (e.g. age, sex, percentage of females), study design (cross-sectional or longitudinal MRI, duration between measurements of activity levels and MRI), MRI analyses (e.g. voxel-based morphometry/region-of-interest, WM lesion assessments), activity levels (e.g. type of activity, life-time period of activity engagement, questionnaire administered), aspects of GM and WM measured (i.e. GM volume, WM volume, WM microstructure, WM lesions) and the findings reported (statistically significant results as indicated by $p < .05$, direction of association/group differences observed, co-variates controlled for).

Due to substantial inter-study heterogeneity in the definitions of cognitive and social activities used, we evaluated the set of activities that an individual study had measured against the classifications of these activity sub-types (proposed by Seider et al. 2016; Table 2.1) and re-categorized them accordingly. For the table of results, studies are divided into cross-sectional and longitudinal MRI, where the former consists of a single MRI session and the latter integrates multiple MRI assessments. To improve comparability among the reviewed studies, age- and sex-adjusted analyses are reported in the tables of results, where possible. The results of these analyses following further co-variate adjustments (e.g. medical history, body mass index), can be found in the footnotes of each table. If, however, the outcome of age- and sex-controlled analyses had not been included in an article, we instead present their fully adjusted analyses in the tables. Finally, regions found to be significantly associated with activity engagement are grouped based on the major lobe or tract of the brain they are contained within (e.g.

frontal, temporal, parietal, occipital and limbic).

To be included in the meta-analysis, studies drawn from the systematic review were required to meet the additional criteria of having performed region-of-interest (ROI) analyses. Voxel-based-morphometry (VBM) studies were excluded as these could introduce substantial bias and are more suitable for alternative methods (e.g. image- or coordinates-based; Salimi-Khorshidi et al., 2009). A meta-analysis was not conducted for local WM volume, as only VBM studies had assessed this outcome. Similar to previous publications (Kempton et al., 2008; Sexton et al., 2013), a meta-analysis was only carried out on a particular lobe, subcortical structure or tract, if it had been examined by at least three studies. This threshold was not met by studies that had examined white matter microstructure (WMM) or GM volume within the different lobes, hence their results are only considered in the systematic review. Further, we could not directly examine the separate effects of cognitive and social activities due to the small number of studies published to date. The meta-analysis therefore examines the *combined* effects of cognitive and social activities. Since Vemuri (2012) and Vemuri (2016) had overlapping samples, only the former was included in the analysis, as it contributed a larger number of participants.

Table 2.1 Activity definitions. These definitions are proposed by Seider et al. (2016) and were used to categorize studies in the systematic review and meta-analysis.

Cognitive activities	Social activities
Using a computer	Visiting family or friends
Doing arts and crafts	Visiting a senior centre
Going to the cinema, concert, lecture or sport event	Volunteering
	Attending church
Playing a musical instrument	Participating in groups or clubs
Reading	Playing cards or board games with others
	Shooting pool or billiards

Comprehensive Meta-Analysis (version 3.3, © November 20 2014, Biostat Inc., Englewood, NJ) was used to analyze the data. Sample sizes, p-values and the direction of associations were entered. The program calculated correlation coefficients based on the parameters provided, which were transformed into Fisher's Z for pooling before being converted back to correlation coefficients for reporting purposes. Fisher's r-to-z transformation was used as it provides a less biased summary index when the number of included studies is small (Silver and Dunlap, 1987). Pooled effect sizes are presented as correlation coefficients to improve their interpretability (Borenstein et al., 2009). To calculate these, *random effects models* were used to allow for inter-study variation and generalization to be made beyond the studies included (Borenstein et al., 2010). Cochrane's Q was used to evaluate inter-study heterogeneity, and publication bias was assessed using funnel plots and Begg & Mazumdar rank correlations test (Begg and Mazumdar, 1994). Authors were also contacted for further information on their analyses to ensure that as many studies as possible were included in this review. If exact p-values could not be obtained, we used the conservative estimate of 0.04 when a p-value within an article had been reported as <0.05 (Sexton et al., 2011). Conversely, a study that reported a non-significant finding as $p > 0.05$ was estimated as $p = 0.5$. When the direction of a reported association could not be determined, the study was excluded. As a minimum of ten studies are required to perform sub-group analyses and meta-regressions (Higgins & Green, 2011), we were unable to assess the extent to which study design and sample characteristics moderated the examined effects.

2.2.5 Quality Assessment

Study quality was evaluated according to the Quality Assessment Tool for Observational

Cohort and Cross-sectional Studies (NIH, 2014). This tool consists of fourteen questions, which assess several potential sources of bias in a study. Areas covered include assessment of measure validity, the suitability of the study design to address a given research question, the extent to which the sample is representative of the population of interest and whether key confounders are accounted for in the analyses. Two independent raters (MA and ND) rated each study as 'Good', 'Fair' or 'Poor'. Any disagreements on the quality rating of a study were resolved through discussion.

2.3 Results

The number of studies yielded at each stage of the search is displayed in Figure 2.1. A total of eighteen studies were included in this review with the sample characteristics and details of the design of each included study displayed in Table 2.1.

Figure 2.1 Flow chart of study selection and exclusion.

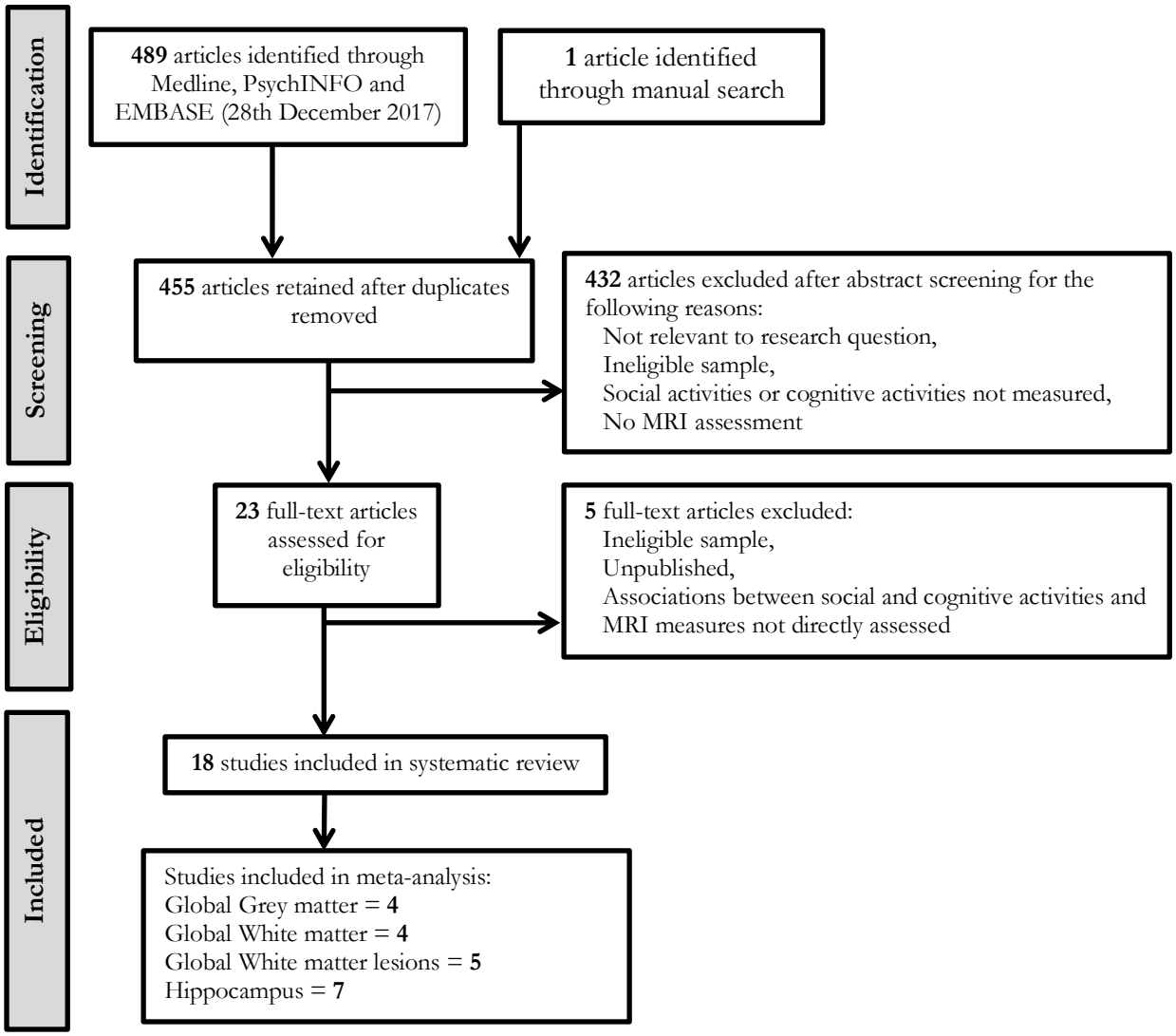


Table 2.2 Sample characteristics and design of included studies.

Study	N	Mean Age ± SD	% Female	Design	Activity Assessment	Quality Rating
Arenaza-Urquijo et al. (2016)	45	71.9±6.6	51.1	T1: MRI, CA+SA	25-item CAS (Wilson et al., 2003)	Good
Arfanakis, et al. (2016)	379	82±7	77	T1: MRI, CA+SA	39-item CAS (Wilson et al., 2005)	Good
Bartrés-Faz, et al. (2009)	15	68.3±4.5	73.3	T1: MRI, CA+SA	Study specific questionnaire (Solé-Padullés et al., 2009)	Good
Bennett, et al. (2006)	106	85.2±2.9	48.1	T1: CA, SA T2: MRI; 1-month interval	Kilsyth Disability Rating Scale (Akhtar et al., 1973)	Good
Foubert-Samier, et al. (2012)	331	76.1±3.9	57.4	T1: MRI, CA, SA	30-item study-specific questionnaire	Good
Gidicsin, et al. (2015)	186	74.4±6	55	T1: MRI, CA+SA	25-item CAS (Wilson et al., 2003)	Good
Gow, et al. (2012)	691	72.7±0.7	47.3	T1: CA+SA; T2: MRI, 3.2 year interval	Study-specific questionnaire	Good
Hafsteinsdottir, et al. (2012)	4304	76.1±5.4[a]	58.5	T1: MRI, CA+SA	10-item study-specific questionnaire	Good
James, et al. (2012)	348	65.2±7.9	0	T1: MRI, SA; T2: MRI, SA; 5 year interval	EFP (Glass, 1998)	Good
Köhncke, et al. (2016)	442	85.1±4.5	68.1	T1: MRI, CA, SA; T2: MRI, CA, SA; 3 year interval	Study-specific questionnaire	Good
Schultz, et al. (2015)	329	60.3±6.3	69	T1: CA+SA; T2: MRI; 1.33 year interval	Modified version of 25-item CAS (Wilson et al., 2003)	Good
Seider, et al. (2016)	65	71.4±8.9	56.9	T1: MRI, CA, SA	CHAMPS (Stewart et al., 1997)	Good
Suo, et al. (2012)	151	80.8±4.6	55.6	T1: MRI; T2: MRI, CA+SA; 2 year interval	LEQ (Valenzuela and Sachdev, 2007)	
Valenzuela, et al. (2008)	37	70.3±5.8	56.9	T1: MRI; T2: MRI, CA+SA; 3 year interval	LEQ (Valenzuela and Sachdev, 2007)	Good
Vaughan, et al. (2014)	393	81.2±4.3	100	T1: MRI, CA+SA	CAS (Wilson et al., 1999)	Good
Vemuri, et al. (2012)	515	79±not reported	43	T1: CA+SA; T2: MRI; 1.5 year interval	Study-specific questionnaire	Good
Wirth, et al. (2014)	92	75.2±5.6	58	T1: MRI, CA+SA	25-item CAS (Wilson et al., 2003)	Good

Abbreviations – CA = Cognitive Activity; CA+SA = Composite Measure of Cognitive and Social Activities; CAS = Cognitive Activity Scale; CHAMPS = Community Healthy Activities Model Program for Seniors; EFP = Enacted Function Profile; LEQ = Lifetime of Experiences Questionnaire; MRI = Magnetic Resonance Imaging; N = Number; SA = Social Activity; SD = Standard Deviation; T1 = Time Point 1; T2 = Time Point 2

[a] The original study reported sub-group means and SDs, hence, the overall mean age and SD for the sample were calculated (Higgins & Green 2008). We also present the overall percentage of females in Hafsteinsdottir, et al.'s (2012) study.

2.3.1. Grey Matter (GM)

2.3.1.1 Global GM Volume

Table 2.3 Cross-sectional MRI studies that have investigated the association between cognitive and social activities and global GM volume.

Study	Period of life	Activity	Results	Co-variates
Foubert-Samier et al. (2012)	Mid-life	CA[a]	n.s	Age, sex, education, APOE4
	Current	CA	n.s.	
	Mid-life	SA	n.s.	
	Current	SA	n.s.	
Gow et al. (2012)	Current	CA+SA	n.s.	Age, sex
Hafsteinsdottir et al. (2012)	Current	CA+SA	↑[***b]	Age, sex, education, BMI, CHD, hypertension, MCI, diabetes, smoking status
James et al. (2012)[c]	Current	SA	↑	Age, education, ICV, ethnicity/ race, diabetes, hypertension, handedness, group (former lead workers/ controls)
Vaughan et al. (2014)	Current	CA+SA	n.s.	ICV

[***]$p<0.0001$

Abbreviations- APOE4 = Apolipoprotein E ε4; BMI = Body Mass Index; CA= Cognitive Activity; CA+SA = Composite Measure of Cognitive and Social Activities; CHD = Coronary Heart Disease; ICV = Intracranial Volume; MCI = Mild Cognitive Impairment; n.s = Not Significant; ROI = Region-of-Interest; SA = Social Activity; VBM = Voxel-based Morphometry; ↑ refers to a positive relationship between activity engagement and whole-brain measures of GM volume.

[a]These authors categorized mid-life and current CA into those that were cognitively stimulating and those that were not. None of these combinations of variables (i.e. mid-life/ current, stimulating/non-stimulating CA) resulted in significant associations with whole-brain GM volume.

[b]Hafsteinsdottir et al. (2012) sub-divided their sample into 4 groups, to represent different levels of leisure activity engagement. Here, ↑ demonstrates the finding that participants in the highest quartile exhibited significantly greater global GM, compared to those in the lowest quartile.

[c]While James et al. (2012) employed a longitudinal MRI design, their primary analysis was cross-sectional, hence, these results are displayed in the above table. The outcome of their secondary analyses, which investigated associations between activity engagement and global GM volume across a 5-year interval are considered, in the main text.

Five cross-sectional MRI studies have examined the relationship between current levels of activities and global GM volume (Table 2). Three studies (Foubert-Samier et al., 2012; Gow et al., 2012a; Vaughan et al., 2014) did not detect any associations between these variables. One study (James et al., 2012) found that global GM volume positively correlated with social engagement levels, but found no association between changes in total GM volume and activity levels at 5-year follow-up. In group comparisons, adults who most frequently participated in socially- and cognitively-demanding activities exhibited greater

global GM volume when compared to those who were the least active in the cohort (Hafsteinsdottir et al., 2012).

A meta-analysis was conducted on four of these studies (pooled n = 5718), which revealed that there was no association between late life leisure activity levels and global GM volume ($p = 0.185$, Figure 2.2). Significant inter-study heterogeneity was, however, detected ($Q = 9.123$, $p = 0.028$, $I^2 = 67.117$). Visual inspection of a funnel plot (Figure 2.3) and a non-significant result from the Begg & Mazumdar rank correlation test ($\tau = 0.167$, two-tailed $p = 0.734$) suggested that there was no substantial publication bias.

Figure 2.2 Effect sizes (correlation coefficient) for total GM volume: No significant association between activity levels and global GM volume.

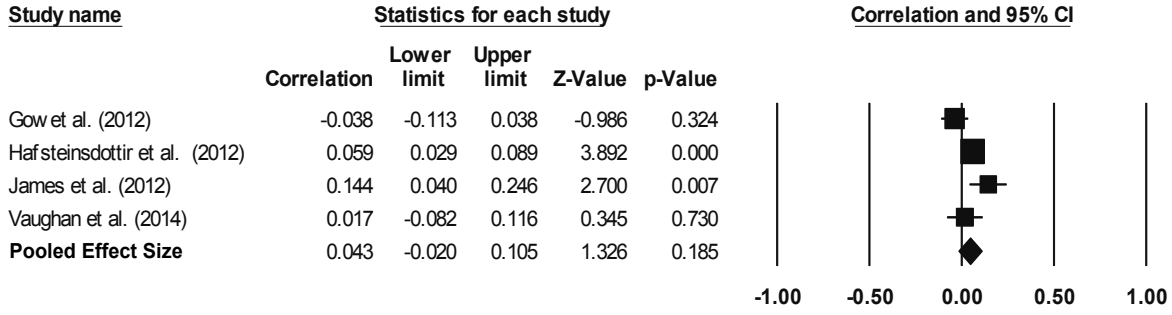
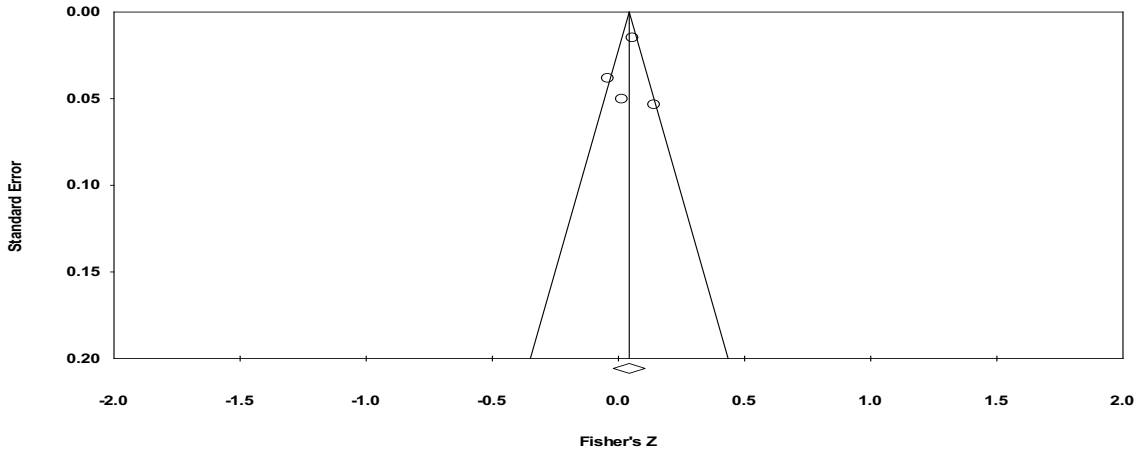


Figure 2.3 Cognitive and social activity levels and global grey matter volume: a funnel plot of standard errors plotted against Fisher's Z.



2.3.1.2 Local GM Volume

Table 2.4 presents the results of the twelve studies that have examined the relationship between non-physical activity participation and local GM volume. There were inter-study variations in the type of MRI analysis employed (i.e. VBM or ROI). Several of the reviewed ROIs studies reported associations between activity engagement and GM volume that spanned all major lobes of the brain (James et al., 2012; Schultz et al., 2015; Seider et al. 2016). Among the cross-sectional VBM studies identified, late life cognitive and social activity participation have also been linked to GM volume in the frontal, parietal, temporal and occipital lobes (Arenaza-Urquijo et al., 2016; Bartres-Faz et al., 2009). In their voxel-wise analyses, James et al. (2012) additionally found that more frequent current participation in social activities correlated with greater temporal and parietal GM volume. One cross-sectional VBM study (Foubert-Samier et al., 2012), however, did not report any significant relationships between local GM volume and CA and SA participation during either mid-life or late life.

The subcortical structure most commonly assessed was the hippocampus. While null findings have been reported (Gidicsin et al., 2015; Schultz et al., 2015; Vemuri et al. 2012; 2016), hippocampal volume has been found to correlate positively with regular late life engagement in cognitive activities (Seider et al., 2016), social activities (Bennett et al., 2006; James et al., 2012) or both types of activities (Bennett et al., 2006; Valenzuela et al., 2008) in a number of studies. Suo et al. (2012) found that *mid-life, but not current*, activity levels were associated with GM in the hippocampus. Further, Valenzuela and colleagues (2008) reported that participants who regularly undertook leisure activities over their lifetime exhibited less decline in hippocampal volume over three years (3.6%), compared to inactive individuals (8.3%).

Table 2.4 Cross-sectional and longitudinal MRI studies that have investigated the relationship between activity participation and local GM volume.

Study	MRI Analysis	Period of Life	Activity type	Results	Significant Lobes (Regions)	Co-variates
Cross-sectional Studies						
Arenaza-Urquijo et al. (2016)	VBM	Current	CA+SA	↑**	Frontal (Middle frontal gyri), Parietal, Temporal (Parahippocampal gyrus, Inferior Temporal Gyrus, Superior Temporal Gyrus, Temporal Pole) Occipital (Angular Gyrus), Limbic (Caudate, Insular Cortex)	Age, sex[a]
Bartrés-Faz et al. (2009)	VBM	Life-time	CA+SA	↑	Frontal (Superior Frontal Gyrus, Medial Frontal Gyrus); Parietal (Supramarginalis Gyrus)	Age, sex, MMSE
Bennett et al. (2006)	ROI	Current	CA (reading) SA (socializing)	n.s. ↑	 Limbic (Hippocampus)	Age, sex, education
Foubert-Samier et al. (2012)	VBM	Mid-life Current Mid-life Current	CA[b] CA SA SA	n.s. n.s. n.s. n.s.		Age, sex, education, APOE4, laterality, ICV
Gidicsin et al. (2015)	ROI	Current	CA+SA	n.s.		Age, education, APOE4, NART IQ, past CA, pedometer assessed total walking speed
James et al. (2012)	ROI VBM	Current Current	SA SA	↑ ↑	Temporal, Occipital Temporal, Parietal	Age, education, ethnicity/ race, diabetes, hypertension, handedness, group (former lead workers/ controls), ICV
Schultz et al. (2015)	ROI	Current	SA (games) CA+SA	↑ n.s.	Frontal (Middle Frontal Gyrus), Limbic (Posterior and Anterior Cingulate)	Age, sex, time interval between CAS and MRI, ICV
Seider et al. (2016)	ROI	Current	CA	↑	Frontal, Parietal, Temporal, Occipital, Limbic (Thalamus, Caudate, Hippocampus, Amygdala)	Education

Study	MRI Analysis	Period of Life	Activity type	Results	Significant Lobes (Regions)	Co-variates
Cross-sectional Studies						
Suo et al. (2012)	VBM	Early-life	CA+SA	n.s.		Age, sex, cardiovascular risk factor scale, PA, ICV
		Mid-life	CA+SA	↑[c]	Limbic (Hippocampus)	
		Current	CA+SA	n.s		
Vemuri et al. (2012)	ROI	Current	CA+SA	n.s.		Age, sex
Longitudinal Studies						
Valenzuela et al. (2008)	ROI	Life-time	CA+SA[c]	↑	Limbic (Hippocampus)	Age, sex, hypertension, ICV
		Life-time	CA+SA	↓	Limbic (Hippocampal atrophy)	
		Mid-life	CA+SA	↓	Limbic (Hippocampal atrophy)	
		Late life	CA+SA	↓	Limbic (Hippocampal atrophy)	
Vemuri et al. (2016)	ROI	Mid-life	CA+SA	n.s.		Age, sex, education, occupation, APOE4, mid-life PA

Abbreviation –APOE4 = Apolipoprotein E ε4; CA = Cognitive Activity; CA+SA= Composite Measure of Cognitive and Social Activities; GM = Grey Matter; ICV = Intracranial volume;

n.s. = not significant; MMSE = Mini Mental State Examination; MRI = Magnetic Resonance Imaging; NART = National Adult Reading Test; n.s. = Not Significant; PA = Physical Activity;

ROI = Region-of-Interest; SA = Social Activity; VBM = Voxel Based Morphometry; ↑ refers to a positive relationship between activity engagement and local measures of GM volume. ↓ indicates an inverse association between participation in leisure activities and hippocampal atrophy.

$^{**}p<0.001$

[a] After additionally co-varying for late life PA, the following regions remained significantly related to CA: Frontal (middle frontal gyrus) Parietal (precuneus cortex), Temporal (parahippocampal gyrus, temporal pole), Occipital (angular gyrus) Limbic (caudate, insular cortex).

[b] In this study, mid-life and current CA were examined separately, which were further separated into those that were cognitively stimulating and those that were not. There were no significant associations between any combinations of variables (i.e. mid-life/ current, stimulating/non-stimulating CA) and local GM volume.

[c] For Suo et al., ↑ demonstrates that participants with high mid-life LEQ scores (i.e. a composite score reflecting high educational and occupational attainment and frequent activity engagement) exhibited greater GM in the hippocampus, compared to participants with low mid-life LEQ scores.

A meta-analysis was conducted using seven of the abovementioned ROI studies that had examined the hippocampus (pooled n = 1455), to reveal a small, yet significant effect size of 0.097 (95% confidence interval (CI) = 0.017 – 0.176, p = 0.017, Figure 2.4). Significant inter-study heterogeneity was also detected (Q = 12.919, p = 0.044, I^2 = 53.557). Publication bias appeared to be absent, as shown by a funnel plot (Figure 2.5) and a non-significant Begg & Mazumdar rank correlation test (τ = 0.286, two-tailed p = 0.368).

Figure 2.4 Effect sizes (correlation coefficient) for hippocampal volume: Higher levels of leisure activities are associated with greater hippocampal volume.

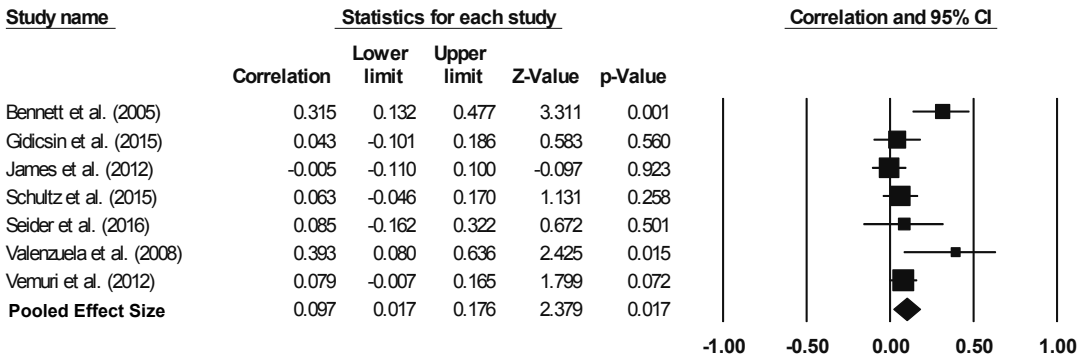
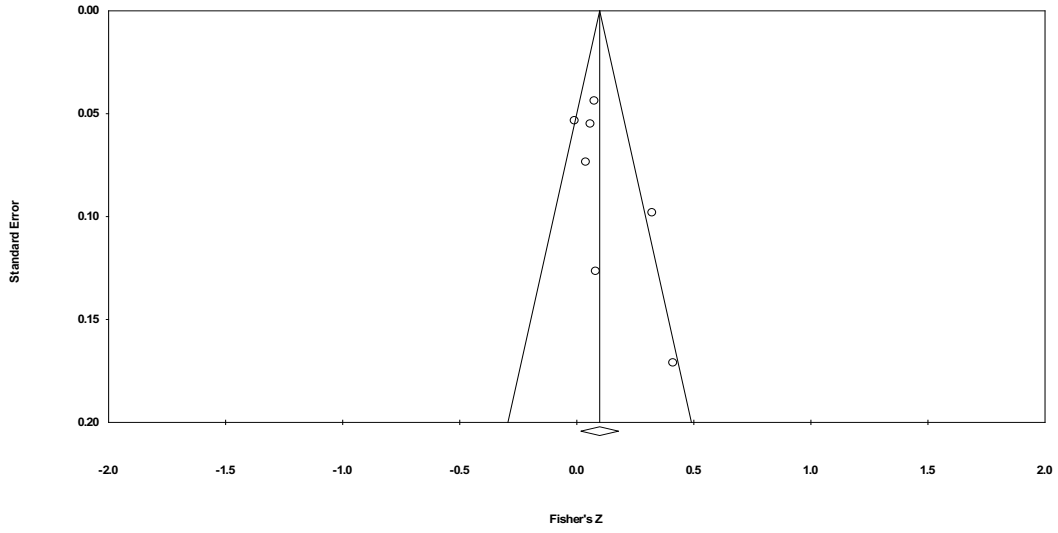


Figure 2.5 Leisure activities and hippocampal volume: a funnel plot of standard errors plotted against Fisher's Z.



2.3.2 White Matter (WM)

2.3.2.1 Global WM Volume

Table 2.5 Findings of cross-sectional MRI studies that have addressed the relationship between activity levels and global WM volume.

Study	MRI Analysis	Period of Life	Activity Type	Results	Co-variates
Bennett et al. (2006)	ROI	Current	CA (reading) SA (socializing)	n.s. n.s.	Age, sex, education
Foubert-Samier et al. (2012)	VBM	Mid-life Current Mid-life Current	CA[a] CA SA SA	n.s. n.s. n.s. n.s.	Age, sex, APOE4, laterality, ICV
Gow et al. (2012)	ROI	Current	CA+SA	↑	Age and sex[a]
Hafsteinsdottir et al. (2012)	ROI	Current	CA+SA	↑***[b]	Age, sex, education, BMI,CHD, hypertension, MCI, diabetes, smoking status
James et al. (2012)	VBM	Current	SA	n.s.	Age, education, ICV, ethnicity/race, diabetes, hypertension, handedness, group (former lead workers/ controls)
Vaughan et al. (2014)	ROI	Current	CA+SA	n.s.	ICV

Abbreviations – APOE4 = Apolipoprotein E ε4; BMI = Body Mass Index; CA = Cognitive Activity; CA+SA = Composite Measure of Cognitive and Social Activities; CHD = Coronary Heart Disease; SA = Social Activity; ICV = Intracranial volume; MCI = Mild Cognitive Impairments; n.s = Not Significant; ↑ demonstrates that increasing levels of activity engagement are associated with greater global measures of WM volume.

***$p<0.0005$

[a] Foubert-Samier and colleagues (2012) evaluated mid-life and current CA individually, and divided CA into either cognitively stimulating or not stimulating activities. There were no significant associations between any combinations of variables (i.e. mid-life/ current, stimulating/non-stimulating CA) and whole-brain WM volume.

[a]After additional adjustments were made for IQ at the age of 11 and social class, this association became non-significant.

[b]These authors divided the cohort into quartiles according to overall leisure activity engagement levels. In this instance, ↑ indicates that participants in the lowest quartile of activity engagement had significantly smaller WM volume, compared to participants who were in the highest active quartile.

Six studies have investigated the cross-sectional relationship between late life participation in cognitive and social activities and global assessments of WM volume. As shown in Table 2.5, the results of four of these studies (Bennett et al., 2006; James et al., 2012; Foubert-Samier et al., 2012; Vaughan et al., 2014) were not significant, with one study also failing to find an association with mid-life cognitive and social engagement (Foubert-Samier et al., 2012). When controlling for age and sex, Gow and colleagues (2012) reported that non-physical leisure activities in late adulthood were positively associated with normal appearing WM volume across the brain. However, this association was no longer significant after accounting for additional co-variates, including childhood IQ, occupation and medical history. The largest study published in this area to date (n = 4304; Hafsteinsdottir et al., 2012), found that older adults who were most regularly engaged in intellectually and socially stimulating activities had higher levels of total WM volume, compared to individuals who were the least engaged.

A meta-analysis of four studies (pooled n = 5736) revealed a significant and small effect size of 0.054 between current activity levels and global WM volume (95% CI = 0.028 – 0.080, $p < 0.001$, Figure 2.6). Tests for heterogeneity ($Q = 2.75$, $p = 0.432$, $I^2 = 0.000$) and publication bias, as assessed by a funnel plot (Figure 2.7) and the Begg & Mazumdar rank correlation test, were not significant ($\tau = 0.500$, two-tailed $p = 0.308$).

Figure 2.6 Effect sizes (correlation coefficient) for total WM volume: a positive relationship between cognitive and social activity levels and whole-brain WM volume.

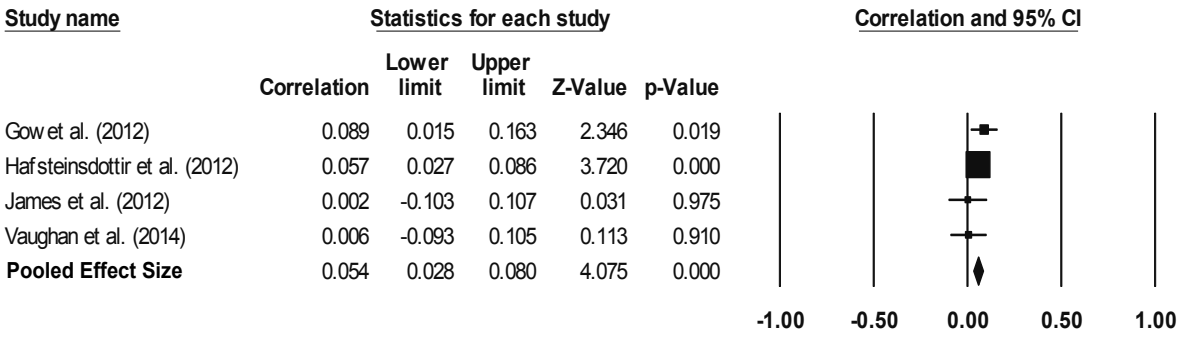
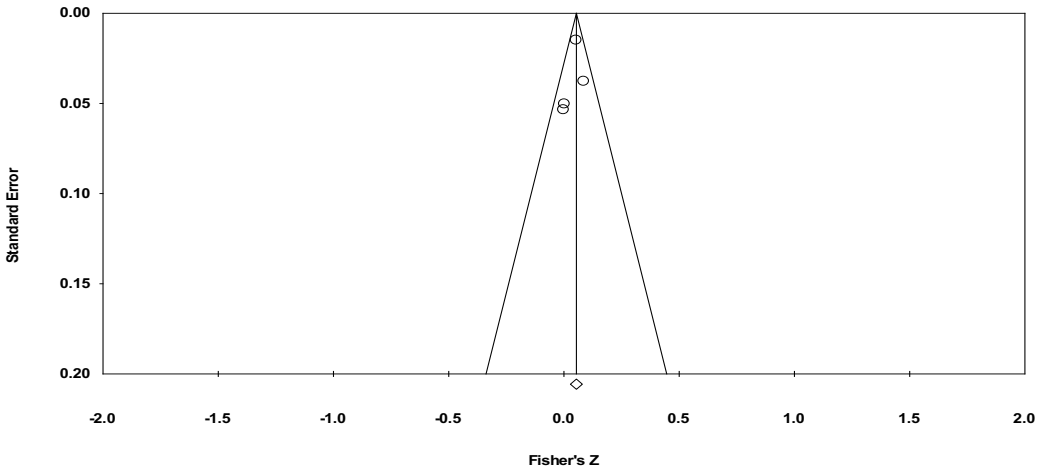


Figure 2.7 Cognitive and social activity participation and global white matter volume: a funnel plot of standard errors plotted against Fisher's Z.



2.3.2.2 Local WM Volume

Two studies examined regional measures of WM volume in relation to activity engagement (Table 2.6). While one of these studies reported null findings for mid-life and current activity levels (Foubert-Samier et al., 2012), the second study identified a positive cross-sectional relationship between current social activity participation and WM volume of the corpus callosum (James et al., 2012).

Table 2.6 The results of cross-sectional MRI studies that have assessed associations between activity levels and region-specific measures of WM volume.

Study	MRI Analysis	Period of Life	Activity Type	Results	Significant Tracts	Co-variates
Foubert Samier et al. (2012)	VBM	Mid-life Current Mid-life Current	CA[a] CA SA SA	n.s. n.s. n.s. n.s.		Age, sex, APOE4, laterality, ICV
James et al. (2012)	VBM	Current	SA	↑	Corpus Callosum	Age, education, ICV, ethnicity/ race, diabetes, hypertension, handedness, group (former lead workers/ controls)

Abbreviations – APOE4= Apolipoprotein E ε4; CA = Cognitive Activity; CA+SA = Composite Measure of Cognitive and Social Activities; n.s = Not Significant; SA = Social Activity; ICV = Intracranial volume; ↑ demonstrates that increasing levels of SA engagement are associated with greater levels of local WM volume. [a]CA engagement was not only divided into mid-life and late life but also further separated into sub-categories stimulating and not stimulating. No associations between any combination of variables were significant (i.e. mid-life/late life, stimulating/ not-stimulating CA) and local WM.

2.3.2.3 Global WM Lesions

In total, seven studies have investigated the relationship between activity participation and whole-brain assessments of WM lesions (Table 2.7). One study found a positive cross-sectional correlation between life-time activity levels and global WM lesion volume, and further analyses indicated that mid-life and current activity levels were individually related to this outcome, although activity levels accumulated over a life-time was not (Wirth et al., 2014). Another study suggested that participants in the highest activity engagement quartile had lower volumes of WM hyperintensities (a difference of 12%), when compared to the least active quartile (Hafsteinsdottir et al., 2012). A further study did not detect any cross-sectional associations between activity engagement and WM lesions (Köhncke et al., 2016). It did, however, find that declines in activity engagement over a three-year period were related to longitudinal increases in whole-brain WM lesions volume (Köhncke et al., 2016). Four studies reported a lack of association between current or life-time levels of activity

participation, WM lesion volume or severity rating (Bennett et al., 2006; Gow et al., 2012a; Valenzuela et al., 2007; Vaughan et al., 2014).

Table 2.7 Findings of cross-sectional and longitudinal studies that have investigated whether activity levels are related to whole-brain WM lesions.

Study	WM lesions Outcome	Period of Life	Activity Type	Results	Co-variates
Cross-sectional Studies					
Bennett et al. (2006)	Periventricular WM lesions	Current	CA (reading) SA (socializing)	n.s. n.s.	Age, sex and education
Hafsteinsdottir et al. (2012)	WM lesion volume	Current	CA+SA	↓**[b]	Age, sex, education, BMI CHD, hypertension, MCI, diabetes, smoking status
Gow et al. (2012)	WM lesion volume (%ICV) WM lesion severity[a]	Current Current	CA+SA CA+SA	n.s. n.s.	Age and sex
Vaughan et al. (2014)	WM lesion volume	Current	CA+SA	n.s.	ICV
Wirth et al. (2014)	WM lesion volume (ICV adjusted)	Early-life Mid-life Current Life-time	CA+SA CA+SA CA+SA CA+SA	↓ ↓ ↓ n.s.	Age, sex and education
Longitudinal Studies					
Köhncke et al. (2016)	WM lesion volume	Current	CA (baseline) CA (change) SA (baseline) SA (change)	n.s. n.s. n.s; ↓	Age, sex and education
Valenzuela et al. (2008)	WM lesion volume	Life-time	CA+SA	n.s.	Age, sex, hypertension and ICV

Abbreviations – BMI = Body Mass Index; CA = Cognitive Activity; CA+SA = Composite Measure of Cognitive and Social Activities; CHD = Coronary Heart Disease; SA = Social Activity; ICV = Intracranial volume; MCI = Mild Cognitive Impairments; n.s = Not Significant; ↓ demonstrates that increasing levels of activity engagement are associated with lower levels of global WM lesions.
**$p<0.005$
[a]Fazekas scale was used to rate WM lesions identified in FLAIR and T2-weighted images as either periventricular or deep lesions, separately for both hemispheres. An overall WM lesion score was then calculated for each participant, using these ratings.
[b] For this study, ↓ indicates that participants in the highest activity engagement quartile had significantly greater levels of global WM lesions, relative to individuals in the lowest quartile group.

A meta-analysis of five of these studies (pooled n = 5587) detected a significant effect size of -0.048 (95% CI = -0.090 – -0.006, p = 0.026, Figure 2.8). The test for heterogeneity was not significant (Q = 5.020, p = 0.285, I^2 = 20.314). Further, inspection of the funnel plot (Figure 2.9) and a non-significant Begg & Mazumdar rank correlation test (τ = -0.100, two-tailed p = 0.806) suggested an absence of publication bias.

Figure 2.8 Effect sizes (correlation coefficient) for global WM lesions: Higher activity levels are related to a reduction in whole-brain WM lesion volume.

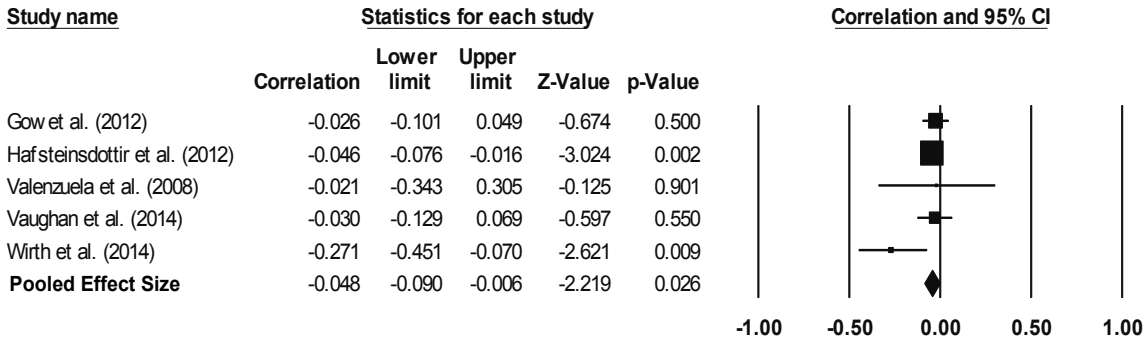
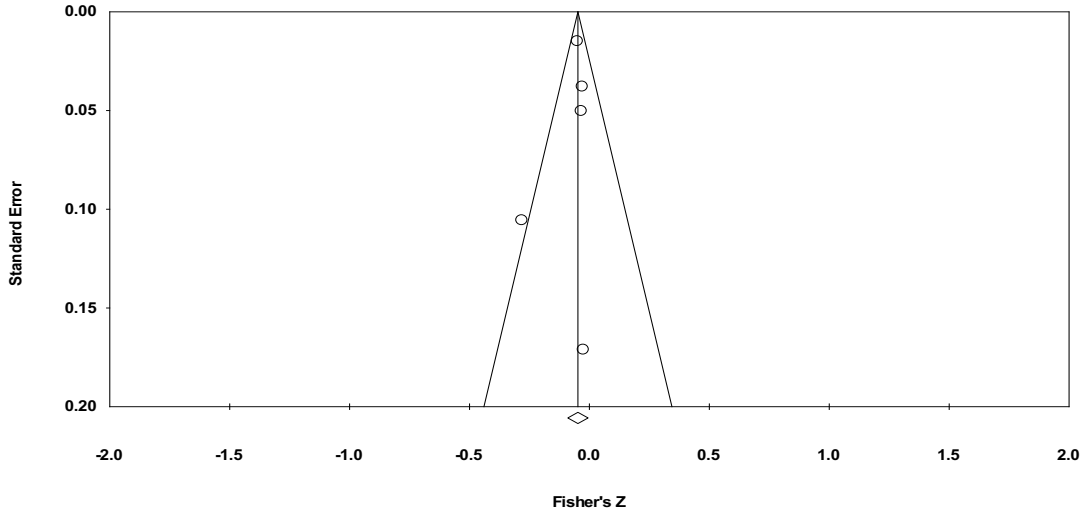


Figure 2.9 Activity participation and global white matter lesions: a funnel plot of standard errors plotted against Fisher's Z.



2.3.2.4 WMM

Three studies (2 cross-sectional, 1 longitudinal; Table 2.9) employed DTI to investigate associations between activity engagement and WMM. One study reported that higher

levels of current cognitive and social activities was related to greater FA in tracts including the left superior and inferior longitudinal fasciculi, fornix and corpus callosum (Arfanakis et al., 2016), and smaller AD and RD in a cluster localized to the thalamus. The second study (Köhncke et al., 2016) found that increasing social engagement over a three-year period was associated with greater FA and smaller MD in the corticospinal tract, with no significant associations to RD or AD in this region. Additionally, increasing participation in low complexity activities (e.g. television watching) was related to greater MD within this tract. Neither cognitive nor social activities significantly correlated with DTI measures in any other of the WM tracts assessed, which consisted of the superior longitudinal fasciculus, forceps major and minor and cingulum cingulate gyrus (Köhncke et al., 2016). The third study did not find a relationship between a composite measure of late life activity participation and global WMM (Gow et al., 2012a).

Table 2.9 Results of cross-sectional and longitudinal DTI studies to have examined associations between cognitive and social activty participation and WMM.

Study	DTI Analysis	Period of Life	Activity Type	Results	Significant Tracts	Co-variates
Cross-sectional Studies						
Arfanakis, et al. (2016)	TBSS	Current	CA+SA	↑FA	Superior and inferior Longitudinal Fasciculi, Fornix, Corpus Callosum Thalamus	Age, sex, education, early-life CA resources, WM lesions
		Current	CA+SA	↓AD, ↓TD, ↓RD		
Gow et al. (2012)	Tractography (12 WM tracts)	Current	CA+SA	FA n.s.		Age, sex
Longitudinal Studies						
Köhncke et al. (2016)	TBSS	Current	CA (baseline)[a]	FA, MD (baseline) n.s.		Age, sex, education
		Current	CA (change)	FA, MD (change) n.s.		
		Current	SA (baseline)	FA, MD (baseline) n.s.		
		Current	SA (change)	↑FA, ↓MD (change)*	Corticospinal	

Abbreviations- AD = Axial Diffusivity; CA = Cognitive Activity; CA+SA = Composite Measure of Cognitive and Social Activities; DTI = Diffusion Tensor Imaging; FA = Fractional Anisotropy; MD = Medial Diffusivity; n.s = Not Significant; RD Radial Diffusivity; SA = Social Activity; TBSS = Tract-Based Spatial Statistics; TD = Trace Diffusivity; WM = White Matter

p<0.01

[a]These authors sub-categorized CA activities as complex (e.g. travelling) or low-level (e.g. watching television). Following this, they used a latent change model to examine the cross-sectional (baseline) and change-change associations between each of these types of activities and FA and MD values. The only significant finding reported was a positive change-change relationship between low complexity CA and MD values.

2.4 Discussion

2.4.1 Summary of Findings

Prompted by epidemiological findings indicating a link between cognitive and social activity levels and cognition in old age, an increasing number of MRI studies have investigated whether socio-intellectual activities directly relate to the structural integrity of the older adult's brain. We aimed to summarize the findings of these MRI studies in the present systematic review and meta-analysis. Through our literature search, we identified eighteen studies that met the eligibility criteria of this review. Overall, the reviewed evidence suggests that composite measures of activities associated with whole-brain volumetric assessments of WM volume and lesions, in addition to regional GM volume across the frontal, parietal, temporal, occipital and limbic lobes, and the hippocampus. Despite the significant findings for regional GM volume, there was no association found between activity levels and global GM volume. Furthermore, the results regarding WMM were inconclusive. Due to an insufficient number of studies published and mixed findings among existing studies, we are unable to make inferences concerning the independent associations of the activity sub-types with GM or WM outcomes. Importantly, for most of the associations identified in the reviewed literature, significant as well as null findings were reported. However, we regard the current evidence as promising and hold the view that future studies will help to further delineate the extent to which cognitive and social activity levels relate to the ageing brain. We next discuss the implications of the reviewed findings for the hypothesized role of leisure activities in brain ageing, the potential neurobiological mechanisms mediating these effects, methodological considerations and avenues for further work.

2.4.2 Do Socio-Intellectual Activities Support Neural Mechanisms?

GM and WM indices are often considered proxies of *brain reserve* (Stern 2002; 2012) among neuroimaging studies (Bartrés-Faz and Arenaza-Urquijo, 2011). The associations found between leisure activities and GM and WM integrity may therefore suggest that *brain reserve* is a potential mechanism underlying the link between socio-intellectual activities and old age cognition. This is unlikely to be the only mechanism at play, as fMRI studies examining leisure activities also suggest a role of *cognitive reserve* in promoting cognitive function, in both healthy ageing and AD (Arenaza-Urquijo et al., 2015; Bartrés-Faz et al., 2009; McDonough et al., 2015). For example, teaching a group of older individuals challenging and novel activities (i.e. digital photography and quilting) over a period of 14 weeks has been reported to improve the modulation of neural activity while performing semantic judgment tasks (McDonough et al., 2015). Being intellectually and socially engaged also appears to relate to reduced signal in the right inferior frontal cortex, interpreted as higher neural efficiency (Bartrés-Faz et al., 2009). A comprehensive review by Arenaza-Urquijo and colleagues (2015) further suggests that leisure activities may directly interact with the development of AD biomarkers (e.g. β-amyloid accumulation (Aβ), hypometabolism and brain atrophy), amongst healthy older adults. Indeed, higher lifetime engagement in cognitive activities has been related to lower levels of cortical Aβ, as measured by [(11)C] labeled Pittsburgh-Compound-B PET imaging (Landau et al., 2012; Wirth et al., 2014). Taken together, there are at least three potential mechanisms underlying the associations found between leisure activities and late life cognition: *brain reserve, cognitive reserve* and slowing down the development of AD-related pathology. While our review suggests a role for *brain reserve*, it is yet to be determined whether these mechanisms are concurrently engaged, or whether one overtakes the other as an individual gets older. Evidently, longitudinal imaging studies combining both structural and functional imaging techniques are needed to address this key outstanding question.

2.4.3 Neurobiological Mechanisms

Several potential candidate processes may support the associations found between socio-intellectual activities and neuroimaging markers of *brain reserve* (overview provided in Figure 2.10). For example, regularly engaging in intellectually- and socially stimulating activities could increase the up-regulation of brain-derived neurotrophic factor (BDNF), a molecule that stimulates neuronal growth and cell proliferation and is known to decline with age (Erickson et al., 2010). Sustained periods of leisure activity might promote higher levels of BDNF, potentially contributing to neurogenesis or prolonging the survival of cells (Valenzuela et al., 2007). Indeed, greater neuronal density in the prefrontal cortex has been found in relation to more cognitively active lifestyles, at autopsy (Valenzuela et al., 2012). Synaptic or dendritic plasticity might also be enhanced, as indicated by increases in the number of synapses of neurons in the rat visual cortex following housing in a complex environment for a month (Briones et al., 2004). Dendritic spines in the somatosensory cortex have also been shown to be sensitive to environmental enrichment, in mice (Jung and Herms, 2014).

BDNF additionally appears to preserve the integrity of WM (Maillard et al., 2016) and promotes recovery following WM damage (Mamounas et al., 2000). This is attributed to the regulatory role of BDNF in the regenerating oligodendrocyte progenitor cells (OPCs), which are essential for the continued renewal of myelin in the central nervous system (Miyamoto et al., 2015; Van't Veer et al., 2009) with the production of OPCs typically attenuated with aging (Miyamoto et al., 2013). Interestingly, exposing adult rats to an enriched environment seems to lead to enhanced numbers of OPCs in the amygdala (Okuda et al., 2009) and corpus callosum (Zhao et al., 2011) relative to non-enriched rats. Although the evidence is limited, the forming of new blood vessels may explain the emerging protective role of cognitive and social activities against WM lesions (Valenzuela

et al., 2007), which develop as a consequence of long-term ischaemia and hypoxia (Prins and Scheltens, 2015). Overall, there are a number of potential mechanisms that may support the reported links between activity and brain structure, including neurogenesis, synaptogenesis, oligodendrogenesis and angiogenesis.

The following sections provide an overview of the current state of the reviewed evidence. We identified four methodological themes within the literature, and these are each addressed in turn.

2.4.4 Methodological Consideration: Demographics and Generalizability

There was substantial heterogeneity within the pool of studies examined, including in their designs and sample characteristics. Nevertheless, all studies received a 'Good' rating suggesting that the quality of the evidence reviewed was highly consistent. We also generally found that participant demographics and recruitment methods were sufficiently described. Most of the included studies were based on secondary analyses of existing cohort data, where typically a subset of the baseline sample was used. Some studies used less than 10% of the original sample (e.g. 3.3%, Köhncke et al. 2016; 8.94%, Vemuri et al. 2016). A caveat of focusing on a such a small sub-group of participants is that it may inadvertently introduce a 'healthy volunteer' bias (Delgado-Rodriguez, 2004), which was observed for studies reporting the characteristics of included and excluded participants. Specifically, participants included in the analytical sample were generally younger, more cognitively intact (as indicated by MMSE scores) and less likely to be diagnosed with hypertension or diabetes (Foubert-Samier, et al. 2012; Hafsteinsdottir et al. 2012). A portion of the reviewed studies also focused on select samples of older adults, such as male ex-employees of a lead manufacturing company (James et al. 2012) or older women (Vaughan et al. 2014). As a consequence, the results reported by these studies are unlikely to generalize to the wider older adult population. The present review was, however, unable

to formally assess the existence of moderating variables using meta-regression, due to the small number of studies included. Nevertheless, future reviews will be able to statistically evaluate whether factors, such as sex or MMSE score, moderate the reported associations as more data becomes available. This will help to clarify whether the review findings do indeed generalize to older adults as a whole or are most relevant for specific sub-groups.

2.4.5 Methodological Considerations: Study Design and Directionality

Cross-sectional MRI was the predominant design employed among the included studies, with only a small number integrating repeat MRI measurements (James et al., 2012; Köhncke et al., 2016; Suo et al., 2012; Valenzuela et al., 2008; Vemuri et al., 2016). The reviewed evidence was also correlational in nature, suggesting that the hypothesis of leisure activities impacting upon brain structure is not the only way to account for the present findings. For example, our results could be explained by progressive brain atrophy causing individuals to withdraw from hobbies, or those with less atrophy being more inclined to participate in an intensive routine of activities. Alternatively, a common third variable (e.g. age) might underlie the associations reported. It should be noted that almost all of the included studies attempted to minimize this risk. For example, age and sex were typically controlled for in analyses, with further adjustments made for other co-variates (e.g. education, apolipoprotein ε4 genotype). Nevertheless, the findings of well-designed RCTs need to be taken into consideration, so as to evaluate thoroughly whether a causal and independent relationship exists between leisure activities and late life brain structure.

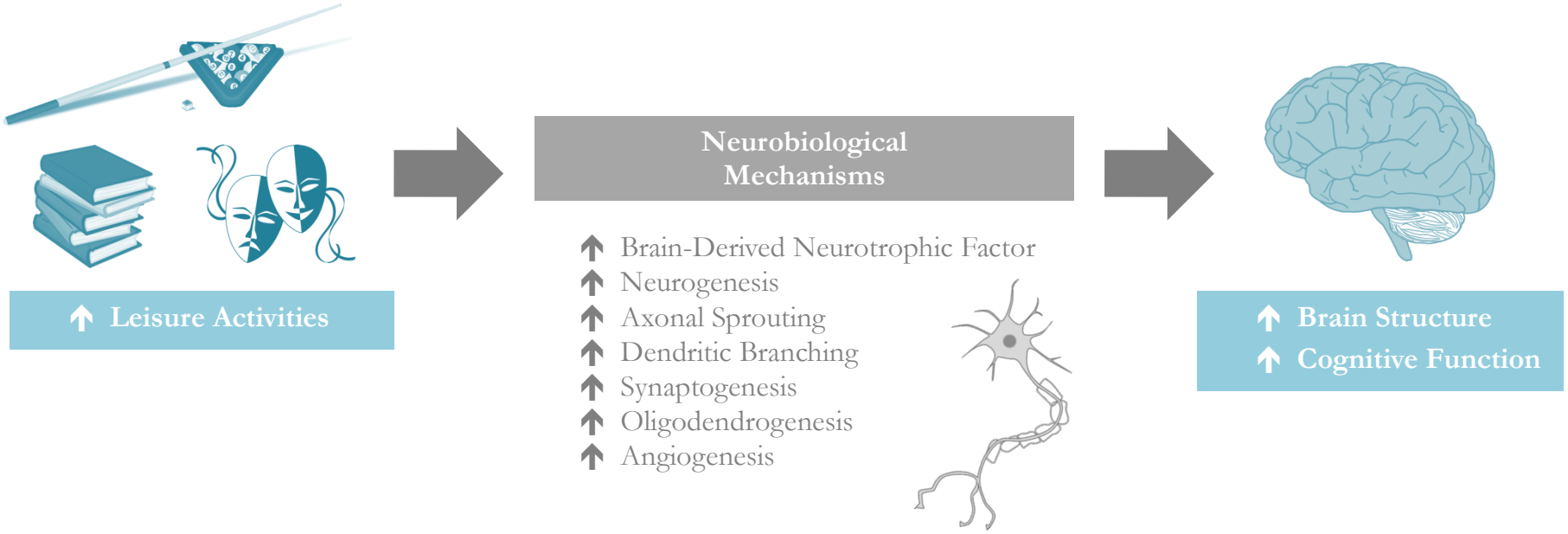
A growing number of RCTs have begun to address the question of causality. Many of these studies indicate that GM enlargements and WM microstructural changes occur after a period of engagement in various mentally challenging tasks, including learning novel color names (Kwok et al., 2011), 3-ball juggling (Driemeyer et al., 2008; Scholz et al., 2009) and training in memory (de Lange et al., 2016) and reasoning domains (Mackey et

al., 2012). More generally, CT has reportedly lead to both structural and functional neural changes in older adults (reviewed in Ten Brinke et al., 2017). Additionally, socializing at a community center over the course of 40 weeks has been reported to increase total brain volume within a sample of elderly adults (Mortimer et al., 2012). Overall, published RCTs provide further support towards the hypothesis that leisure activities directly affect brain structure. These studies are, however, not without their shortcomings. Many RCTs are currently limited by their short follow-up periods and small sample sizes, highlighting the need for large-scale longitudinal studies investigating the effects of leisure activities on the ageing brain.

2.4.6 Methodological Considerations: Measurements of Leisure Activities and Risk of Bias

A key consideration for the review is the risk of measurement error attached to self-report questionnaires, which can be somewhat minimized if the measures used are validated. We generally found that assessments of leisure activities had acceptable psychometric properties. On the other hand, we also came across studies that had employed activity measures without evaluating their validity or reliability. These studies were, however, few in number. The most commonly employed questionnaire was the Cognitive Activities Scale (CAS; Wilson, 1999; 2003; 2005), which is widely validated and has been established in a research setting. This measure collects information on late life activity levels, in addition to retrospectively asking respondents about activity

Figure 2.10 Schematic diagram outlining the proposed neurobiological mechanisms that may support associations between activities and brain reserve and cognition, in old age.



levels across the lifespan (e.g. childhood, early- and mid-adulthood). The CAS is clearly advantageous, as it can be used to probe how activity levels in different lifetime periods relate to various neuroimaging metrics of interest. On the other hand, it is also susceptible to misreporting, particularly among older adults with memory-related impairments (Gow et al., 2017). This limitation may be avoidable if researchers prioritize cohort studies that have collected longitudinal data on activity levels and neuroimaging outcomes (Gow et al., 2017).

Despite efforts to ensure that the questionnaires used in research are psychometrically sound, they remain susceptible to reporting biases including social desirability (Adams et al., 2005) and problems with memory recall (Gow et al., 2017). Unfortunately, there is a scarcity of established objective measures of cognitive and social activities that could easily overcome these problems inherent to self-report instruments. One potential solution may be to employ validated objective assessments used for other health behaviors (e.g. diet, physical activity), within this area of research. We suggest that wearable technology represents a feasible candidate that may be adopted by studies focusing on socio-intellectual activities, in the near future.

A wearable device often takes the form of a small portable camera worn around the neck or a badge worn on shirts, with the main function being to manually or automatically capture photos of the wearer's environment (Bai et al., 2012; Hodges et al., 2006; Sun et al., 2014). This type of technology has been used as an aid for individuals with memory impairments (Hodges et al., 2006), and more recently, as a research tool for the assessment of several modifiable behaviours, including diet and physical activity (Sun et al., 2014). One example of a wearable device is the SenseCam, which has been shown to collect data more accurately (e.g. calorie intake) than detailed self-report assessments (e.g. food diaries; O'Loughlin et al., 2013). Perhaps most importantly for the present review, this device can

be used to differentiate between activities of varying social demands, such as those that are conducted alone or within a public space (with minimal interactions, such as within a shopping center) or that feature direct face-to-face interactions (Doherty et al., 2013). Overall, the described findings suggest that wearable technology may offer an objective way to measure socio-intellectual activities, which may be advantegous over currently used self-report methods.

2.4.7 Methodological Considerations: Defining and Distinguishing between Cognitive and Social Activities

The final, but no less important, methodological theme concerns the definition and operationalization of cognitive and social activities. Generally, these types of activities were not explicitly defined within the reviewed evidence, representing an issue observed more broadly across neuroimaging and epidemiological studies (Cheng, 2016; Hertzog et al., 2009). There were, however, a few exceptions (e.g. Seider et al., 2016). It might be argued that these constructs are self-explanatory and generally agreed upon, hence, no explicit definitions are required. Yet, this did not appear to be the case for the reviewed evidence, as there were considerable differences between studies in the number and type of individual activities used to define activity constructs. Furthermore, activities that involved socializing (e.g. playing games) were sometimes classed as 'social' (Köhncke et al., 2016; Seider et al., 2016) and other times as 'cognitive' (Vemuri et al., 2012; 2016). To address these inter-study inconsistencies, we next outline potential criteria for cognitive and social activities, which have been developed from existing definitions proposed in the broader literature. Authors of future studies could refer to these criteria when deciding on whether a given activity should be categorized as socially or cognitively demanding.

Broadly speaking, previous definitions of cognitive activities have emphasized a key role of information processing (Wilson et al., 2005; Wilson and Bennett, 2003), or otherwise

necessitated that an activity is mentally challenging or stimulating (Hertzog et al., 2009; Seider et al., 2016; Yates et al., 2016). What constitutes mental challenge/stimulation is, however, often left unspecified. The novelty of the information encountered could potentially be considered a defining feature of cognitive complexity (e.g. when learning a language; Hultsch et al., 1999; Jopp and Hertzog, 2010). Yet, novelty alone is not sufficient. For example, a viewer may come across several new facts while watching the television, but only passively take this information in (Cheng, 2010). The *passive* nature of this activity may even partly account for why television watching is emerging as a potentially *harmful* activity for cognition (e.g. Hoang et al., 2016), relative to traditional 'cognitive' activities (e.g. reading; Arfanakis et al., 2016). This would suggest that *actively* engaging with the information encountered is a crucial component for cognitive activities. In other words, it should involve the recruitment of one or several higher-level cognitive domains (e.g. executive function, memory; Hughes, 2010; Jopp and Hertzog, 2010). CT paradigms are indeed based on the premise that cognitive domains can be enhanced through intensive and repeated practice of them (Jak et al., 2013). Overall, it appears that 'mentally challenging/ stimulating' activity should: (1) involve a degree of novelty (e.g. solving a new crossword puzzle, reading a book on an unfamiliar topic) and (2) necessitate one or more higher-level cognitive functions in order to successfully complete it.

Social activities are typically defined as activities undertaken with others, with solitary activities on the other end of the spectrum (e.g. Seider et al., 2016; Singh-Manoux et al., 2003). Although the presence of others is necessary to define social engagement, we argue that, this in itself, is not sufficient. Otherwise, activities intuitively recognized as *not socially demanding*, may be mis-categorized as such. For example, a lecture is usually given to a group of attendees, rather than a single individual. While being a group-orientated activity, 'attending a lecture' is almost exclusively defined as a 'cognitive' rather than 'social' activity

(Schultz et al., 2015; Seider et al., 2016; Vaughan et al., 2014; Vemuri et al., 2016, 2012). This could be attributed to it missing a potentially crucial component of social engagement, i.e. the *direct* interactions between individuals. More generally, these direct interactions could take the form of engaging in a conversation, providing emotional support and shared reminiscing, among other examples. Based on our discussion, we put forward the following criteria for social activities: the (1) presence of others and (2) explicit communication between members participating in the activity.

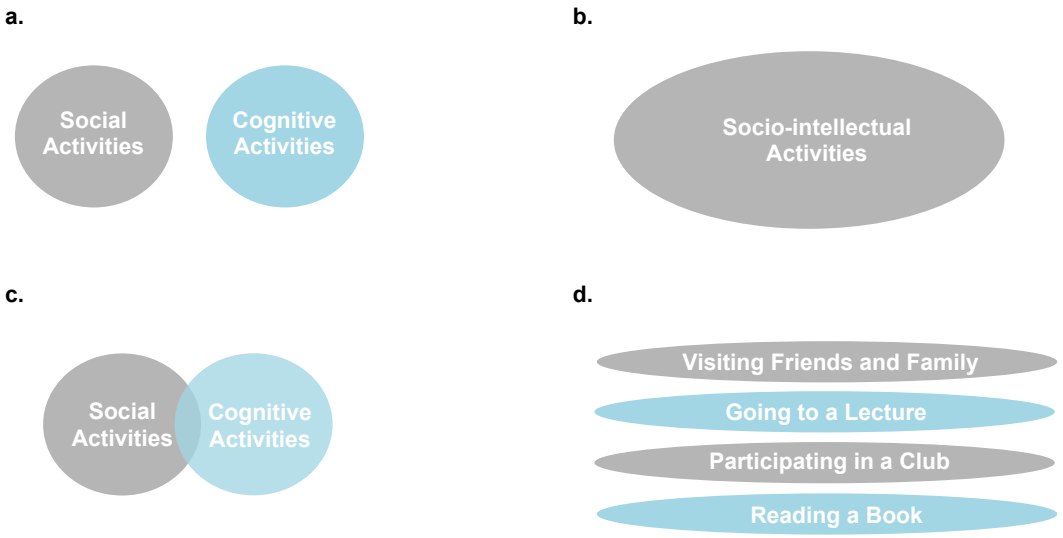
The second methodological issue is the operationalization of socio-intellectual activities. Specifically, the reviewed evidence mainly employed two approaches. The first involves using the distinct categories of cognitive and social activities, where each consists of an independent cluster of activities (a in Figure 2.11). This method was employed by four of the included studies and has the benefit of examining the individual effects of cognitive and social activities. A major disadvantage is that it provides a poor fit for activities with both strong mental and interpersonal components (e.g. playing bridge; Cheng, 2016). Additionally, there was substantial disagreement among the reviewed studies on which particular activities fell under cognitive and social engagement. We sought to reduce these discrepancies by re-categorizing the reviewed studies in accordance with the distinctions of activity sub-types suggested by Seider and colleagues (2016). One alternative to distinguishing between cognitive and social activities is to examine 'socio-intellectual activities' as a singular construct (b in Figure 2.11), which was the method used by thirteen of the reviewed studies. This latter approach is advantageous over the former as it allows for activities to have concurrent social and cognitive demands, reduces inter-study disagreement and examines the combined effects of cognitive and social activities. It is, however, not without its own set of problems. For example, it involves summing across a diverse range of activities, which has the risk of attenuating effects of interest and in

extreme cases, producing null findings (Cheng, 2016). Relatedly, it prevents us from disentangling the potentially independent effects of socially and cognitively demanding activities on the ageing brain. There are two additional methods that are currently underused by studies within this area, which may help to overcome the problems faced by the dichotomous and composite operationalizations of cognitive and social activities. We suggest them as either substitutes or complementary to currently employed approaches.

One of the proposed methods is to operationalize cognitive and social activities as two related, but distinct constructs (c in Figure 2.11). In practice, this could involve rating each activity according to their perceived social and cognitive demands (e.g. low/medium/high), before combining activities with medium-to-high demands into cognitive and social activity constructs. A similar approach was used in one of the reviewed studies (Köhncke et al., 2016) and has also been used in studies examining cognition (Singh-Manoux et al., 2003). This method addresses the problem presented by activities with concurrent cognitive and social demands, as such items could feature in both activity constructs. It also shares a key advantage of the dichotomous method in that it can be used to investigate the independent effects of each activity sub-type. As with all composite measures, however, it still retains the risk of attenuating effects of interests. To address this issue, we suggest that a complimentary approach is applied, if the statistical power of a study allows for it. Specifically, each activity within the cognitive and social activity constructs could be evaluated as independent correlates of the neuroimaging outcomes examined (d in Figure 2.11). Used by two of the included studies (Bennett et al., 2006; Schultz et al., 2015), this method may be particularly informative for intervention development. This is because it has the potential to highlight an activity (or set of activities) especially beneficial for brain health, and therefore identify potential targets for novel interventions. Overall, we propose that future studies should consider using the

abovementioned approaches in their analyses, as they may aid the field in continuing to make sufficient progress towards developing interventions that promote healthy brain aging.

Figure 2.11 Schematic diagrams representing the different methods used to operationalize leisure activities. **a.** Activities are treated as distinct constructs. **b.** social and cognitive activities are combined into a single measure to reflect 'socio-intellectual activities'. **c.** Each activity sub-type is employed as distinct, but related constructs. **d.** Each activity item is examined as an independent correlate of the outcomes of interest.



2.5 Conclusions

In the past decade, a growing number of MRI studies have started to focus on the relationship between leisure activity levels and the ageing brain. Among the reviewed studies, we found that composite measures of socio-intellectual activities were related to global WM (volume and lesions) and hippocampal volume. Moreover, frequent participation in activities correlated positively with regional GM volumes located within all major lobes of the brain. No link was found with global GM volume and studies examining WM microstructure produced inconsistent results. These findings are taken to suggest that leisure activities may contribute to *brain reserve*, with other neuroimaging studies also implicating a role in *cognitive reserve* and the development of AD-related neuropathology. As this field remains in its relative infancy, we propose several

methodological improvements and avenues for further work. These suggestions have included (1) the use of multi-modal imaging and longitudinal RCTs, in addition to (2) wearable technology for the objective measurement of socio-intellectual activities. We also contribute (1) criteria for defining the non-physical sub-types of activities and (2) suggest alternative methods to operationalize these constructs, which could be used by future studies. Overall, the current evidence supports a protective role of cognitive and social activities against the negative effects of ageing on GM and WM structures in the brain, during late life.

CHAPTER 3

Associations Between Late Life Activity Levels, Brain Structure, Functional Connectivity and Cognition in the Whitehall II Cohort

Contents

Abstract 89

3.1 Introduction 91

3.2 Methods 92

3.3 Results 103

3.4 Discussion 111

3.5 Strengths and Limitations 118

3.6 Conclusion 119

Abstract

The systematic review and meta-analysis conducted in the previous chapter provides promising evidence to support a link between socio-intellectual activities and global and region-specific measures of GM and WM integrity. The extent to which cognitive and social activities independently relate to these MRI measures, and whether functional connectivity is at all sensitive to the hypothesized effects of activities is, however, currently unclear. This chapter therefore aimed to evaluate whether *late-life* participation in cognitive and social activities is significantly related to GM volume, WM integrity and resting-state functional connectivity in three age-sensitive resting-state networks, specifically, the default mode network (DMN), frontoparietal network (FPN) and executive control network (ECN). In a sample of 624 members of the Whitehall II Imaging Sub-study[2],

[2] The Whitehall Research team recruited participants and collected the data for this study. I planned, conducted and interpreted the analyses described in this chapter.

participants underwent a 3T MRI scan, battery of cognitive assessments and completed the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire on current activity habits. To address whether there were associations between activities and voxel-wise measures of GM, WM microstructure and resting-state functional connectivity, a series of general linear models were conducted. Linear regressions were also used to investigate associations between activities and global and domain-specific cognition (i.e. executive function, memory and processing speed).

This chapter reports positive associations between late life participation in cognitive activities and performance on tests of global cognition and executive function, after controlling for sociodemographic, lifestyle and health co-variates. This type of activity, however, possessed no associations with MRI measures of GM volume, WM microstructure, WM lesions and resting-state functional connectivity of the ECN, DMN or FPN. Post-hoc analyses suggested that these null findings also extended to other resting-state network (e.g. sensorimotor and visual networks). Social activities, conversely, correlated with total GM volume, but was not linked to cognition.

Overall, this chapter replicates previously reported associations between cognitive activities and cognition, although the absence of any associations with MRI markers of brain structure and functional connectivity may suggest alternative mechanisms may be at play. The null associations between social activities and cognition also raises the question of how clinically meaningful the link reported in prior evidence may be. This chapter ends with a consideration of how longitudinal studies examining *prior* activity levels may provide further insight into the extent to which these activities contribute to old age brain health.

Keywords: Leisure activity, cognitive ageing, Whitehall, cross-sectional, MRI.

3.1 Introduction

The meta-analyses of Chapter 2 demonstrate that, collectively, socio-intellectual activities correlate with greater volumetric measures of global WM and hippocampal volume, and fewer lesions within the WM. However, the evidence is less consistent with regard to the individual effects of these activity sub-types on brain structure and whether these activity types correlate with DTI metrics of WM microstructure. Inter-study differences in how intellectual stimulating and socially engaging activities have been defined further contribute to the 'noise' in the evidence, particularly because there is no standardized approach to categorizing activities into measures of cognitive or social engagement, and little insight into how previous authors have made such decisions. Relatedly, almost all of the reviewed studies opted for a 'mutually exclusive' (Figure a. in 2.11) method, which provides an ill fit for activities exerting both high cognitive *and* social demands. To address these methodological issues, our review encourages future studies to take up approaches that have been underutilized to date – such as treating cognitive and social activities, as dissociable but related constructs (Figure b. in 2.11).

Another issue touched upon in the review chapter was the absence of any resting-state fMRI studies investigating activity-brain associations. This is surprising, as several major resting-state networks have been shown to be sensitive to ageing (Mevel et al., 2011; Sala-Llonch et al., 2015). A key finding here is that intra-network connectivity of networks involved in attention and memory generally decline with age (Ferreira and Busatto, 2013). This has been most consistently observed for the DMN (e.g. Biswal et al., 2010; Ng et al., 2016), with a few studies suggesting that these attenuating age effects also extend to the ECN (Ng et al., 2016) and FPN (Campbell et al., 2012). Considering that decreases in functional connectivity partly accounts for inter-individual variability in cognitive function in older adult samples (Ferreira and Busatto, 2013; Mevel et al., 2011; Sala-Llonch et al.,

2014), it may serve as an important endpoint to consider when examining whether leisure activities contribute to maintaining the ageing brain.

3.1.1 Aims

The aim of this chapter is to evaluate whether *late life* levels of participation in cognitive and social activities independently relate to GM volume, WM microstructure, WM lesions, and functional connectivity of the DMN, ECN and FPN. We also aim to employ an alternate approach to categorizing activities, which allows for a given activity to hold concurrent cognitive and social demands. Based on our previous findings (Anatürk et al., 2018), we expect to find positive associations between activity participation and regional GM volume and WM microstructure and negative links with volumetric measures of WM lesions. We also perform an exploratory analysis of three networks implicated in ageing and cognitive decline (Ferreira and Busatto, 2013; Sala-Llonch et al., 2015), namely, the DMN, ECN and FPN. Due to a lack of evidence, we do not make any predictions about the direction of associations between activities and functional connectivity of these networks. As there are a number of meta-analyses identifying a link between activities and cognition (Evans et al., 2018; Kuiper et al., 2016; Yates et al., 2016), we expect to find that higher cognitive and social activity levels will be associated with higher levels of global cognition, executive function, memory and processing speed.

3.2 Methods

3.2.1 Sample Characteristics

Participants were from the Whitehall II study (Marmot et al., 1991), an on-going prospective occupational cohort study that investigates social gradients in health outcomes.

A total of 10,308 British civil servants, between the ages of 35-55 years (born between 1932-1955), were recruited at baseline (Phase 1, 1985-1988), of whom 6,895 were men.

These participants have provided information on a wide range of demographic, cognitive, lifestyle, genetic and health factors at each assessment phase, with an interval of approximately 5 years between phases (Marmot and Brunner, 2005) More recently, eight hundred participants (12.7%) were randomly selected from Phase 11 (2011-2013) to participate in the Whitehall II Imaging Sub-Study (2012-2016) at the FMRIB Centre, University of Oxford (Filippini et al., 2014). The study received ethical approval from the University of Oxford Central University Research Ethics Committee, as well as the University College London Medical School Committee on the Ethics of Human Research (Committee Alpha, reference: 85/0938). All participants enrolled in this study gave their informed and written consent.

3.2.2 Inclusion/Exclusion Criteria

For a flow chart of the stages of participant inclusion and exclusion, please see Appendix 3.1. In brief, individuals were included in this study if they had completed the questionnaire measuring activity levels and the assessments of cognition, did not have any known diagnoses of neurological disease (e.g. Parkinson's disease or stroke) or signs of major brain abnormalities (e.g. brain cysts), were without MRI contraindications and had provided adequate structural, resting-state and diffusion-weighted images. Those excluded consisted of individuals selected based on their depressive symptoms (n= 30) or who had a self-reported neurological disorder (n = 68), had missing imaging data or poor quality MRI images (n = 58), missing CHAMPS data (n = 2) and missing cognitive data (n = 18).

3.2.3 Cognitive and Social Activity Levels

The Community Healthy Activities Model Program for Seniors (CHAMPS; Stewart et al., 2001) questionnaire was used to measure current activity levels. In brief, respondents were required to indicate their average (1) frequency and (2) duration (hours/ week) of involvement in 40 different activities, over the past month. We considered only the latter

for the present analyses, as it provides a more precise index of engagement levels in activities. For example, a person may report frequent participation in a given activity (e.g. reading) but only engage in it for a few minutes at a time. Responses related to activity duration ranged from 'less than 1 hour' (= 1) to '9 or more hours' (= 6), per week. Based on the original CHAMPS scoring system (Stewart et al., 2001), the raw responses were first recoded (e.g. 1 = 0.5; 6 = 9.75) and items without responses were coded as 0. Cognitive and social demand weightings for each item were then independently assigned by Melis Anatürk (MA), Claire Sexton (CES) and Klaus Ebmeier (KPE), with the categories assigned consisting of 'low' (= 1), 'medium' (= 2) or 'high' (= 3). Initial inter-rater agreement was high, with intra-class correlation coefficients of 0.941 (95% CI = 0.893 – 0.968, social activity ratings) and 0.842 (95% CI = 0.72 – 0.913, cognitive activity ratings). Any item ratings that were discrepant among raters were resolved through subsequent discussion (for agreed upon item ratings, see Appendix 3.2). The duration variables of each activity item were then weighted by their cognitive/social demand score (i.e. 'low' activities = duration*0, 'medium' activities = duration*1, 'high' activities = duration*2), before the sum across all of the items were calculated. This method produced two sub-scores: (a) cognitive and (b) social activity levels, with higher scores indicating greater engagement. Participation in cognitive activities positively correlated with social activity levels (Pearson's r= 0.616, $p < 0.001$).

3.2.4 Cognitive Function

A battery of cognitive tests was administered prior to the MRI brain scan, with a detailed description of each measure available in Appendix 3.3. The cognitive battery was sub-divided based on previous studies (Demnitz et al., 2017; Sexton et al., 2017) which included an assessment of *global cognition* and three key sub-domains: *executive function, memory and processing speed. Global cognition* was assessed using the Montreal Cognitive Assessment

(MoCA, Nasreddine et al., 2005). *Executive function* assessments included sub-scores of the digit span test (forward, backward and sequence; Wechsler, 2008) language fluency (category and verbal; adapted from the Addenbrooke's Cognitive Examination Revised; ACE-III; Hsieh et al., 2013) and part B of the Trail-making test (TMT; Reitan, 1958). Measures of *memory* included the Rey-Osterrieth Complex Figure (RCF; immediate recall, delayed recall and recognition; Osterrieth, 1944) and Hopkins Verbal Learning Test Revised (HVLT-R; total recall, delayed recall and recognition; Brandt, 1991). *Processing speed* was assessed by part A of the TMT (Reitan, 1958) digit coding (Wechsler, 2008) and simple reaction time, choice reaction time, simple movement and movement time (Sahakian et al., 1993) derived from the Cambridge Neuropsychological Test Automated Battery Reaction Time touchscreen task (CANTAB RTI; CANTABeclipse 5.0; Cambridge Cognition Ltd). For the CANTAB and TMT measures, scores were multiplied by -1 so that higher scores indicated better performance.

3.2.5 Demographic and Health Variables

Information about each individuals' sociodemographic, health and lifestyle profile was collected on the date of the MRI scan. Educational level was evaluated on a 5-point scale: (1) no qualifications, (2) O-levels or equivalent (at 16 years), (3) A-levels, college certificate or professional qualification (at 18+ years), (4) degree (BSc, BA), (5) higher degree (MA, MSc, PhD). Body mass index (BMI) was calculated using information on height and weight: (weight [kilograms]/(height [metres])^2. Marital status consisted of a binary variable, reflecting individuals who were either with a partner (married or co-habiting) or without a partner (divorced/ single). Blood pressure was measure twice while participants were in a seated position (OMRON HEM-907; OMRON Healthcare UL Ltd., Milton Keynes). From this, mean arterial pressure (MAP) was computed: ((systolic blood pressure + 2* diastolic blood pressure/3); Sexton et al., 2017). Depressive symptoms was measured

through a self-report assessment, using the Centre for Epidemiological Studies Depression Scale (CES-D; Radloff, 1991). Sleep quality (over the past month) was measured by the Pittsburgh Sleep Quality Index (PSQI, Buysse et al., 1989). Alcohol intake (total units/ per week) was assessed by a set of items specific to the Whitehall II study that asked respondents to indicate their weekly consumption of different types of alcoholic drinks (e.g. wine, beer, spirits). Physical activity was measured with the CHAMPS (Stewart et al., 2001) questionnaire. Using the original MET values for each CHAMPS activity (Stewart et al., 2001) we sub-divided all items of this questionnaire into 'low intensity' (MET value not assigned), 'moderate intensity' (METs ≥ 1 and < 3) or 'high intensity' (METs ≥ 3) physical demand. A weighted summary score was then calculated from self-reported duration in activities classified as moderate and high intensity.

3.2.6 MRI Data Acquisition and Pre-processing

3.2.6.1 MRI Data Acquisition

Scanning was undertaken at the Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), now part of the Wellcome Centre for Integrative Neuroimaging (WIN) - University of Oxford. Full information on the MRI protocol can be found in Filippini et al. (2014). MRI data were collected using either a 3 Tesla Siemens Magnetom Verio (April 2012 – Dec 2015) or a 3 Tesla Siemens Magnetom Prisma (June 2015 – Dec 2016), with a 32-channel head coil.

High resolution T1-weighted images were acquired using a three-dimensional rapid gradient echo sequence with a repetition time of 2530 ms, echo time of 7.37 ms (Prisma: 2.19 ms), flip angle of 7°, 256 mm field of view and 1.0 mm isotropic voxels. Diffusion-weighted images were collected using echo-planar imaging, with 60 diffusion weighted directions (b-value 1500s/mm^2), five non-diffusion weighted images (b-value 0s/mm2)

and a single b0 volume collected in the reversed phase encoded direction. The repetition time was 8900 ms with an echo time of 91.2 ms (Prisma: 91 ms), a field of view of 192 mm, with 2.0 mm isotropic voxels. Resting-state functional images were acquired using multiband echo-planar imaging, with a repetition time of 1300 ms, echo time of 40 ms, flip angle of 66°, field of view of 212 mm and 2.0 mm isotropic voxels. Fluid attenuated inversion recovery (FLAIR) images were used to identify WM hyperintensities (repetition time = 9000ms, echo time = 73 ms, field of view = 220 mm, anisotropic voxels = 0.9 x 0.9 x 3.0 mm).

3.2.6.2 MRI Data Pre-processing

Both the structural and functional images were pre-processed using tools from the FMRIB Software Library (FSL, version 5.0 http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/; Smith et al., 2004) For the analyses examining GM volume, the raw T_1-weighted images were first reoriented to a standard MNI template, bias field corrected, and registered to the MNI template using linear (Jenkinson and Smith, 2001) and non-linear registration (Andersson et al., 2007). Brain tissue was then segmented into GM, WM and CSF using FMRIB's Automated Segmentation Tool (FAST; Zhang et al., 2001) and global volumetric measures of these tissues were extracted. Global GM and WM volumes were adjusted for total intracranial volume. T1-weighted images were brain extracted, GM segmented and then registered to the MNI 152 standard space with non-linear registration (Andersson et al., 2007). These images were averaged and flipped along the x-axis to produce a symmetrical, study-specific GM template. All native GM images were non-linearly registered to the GM template and modulated to correct for local expansions and contractions. The resulting images were smoothed with an isotropic Gaussian kernel with a sigma of 3 mm, using FSL-VBM.

During the initial acquisition of T_1 scans, online corrections for motion were employed (15% of the sample). This was later discontinued after it was determined that it made no substantial improvements to image quality. Initial VBM analyses also indicated that this variable acted as a confounder to the observed results. While we control for this variable in all VBM analyses related to the Whitehall dataset, we will not make any further reference it, due to it being a methodology-related covariate and to help improve the flow of text without repetition.

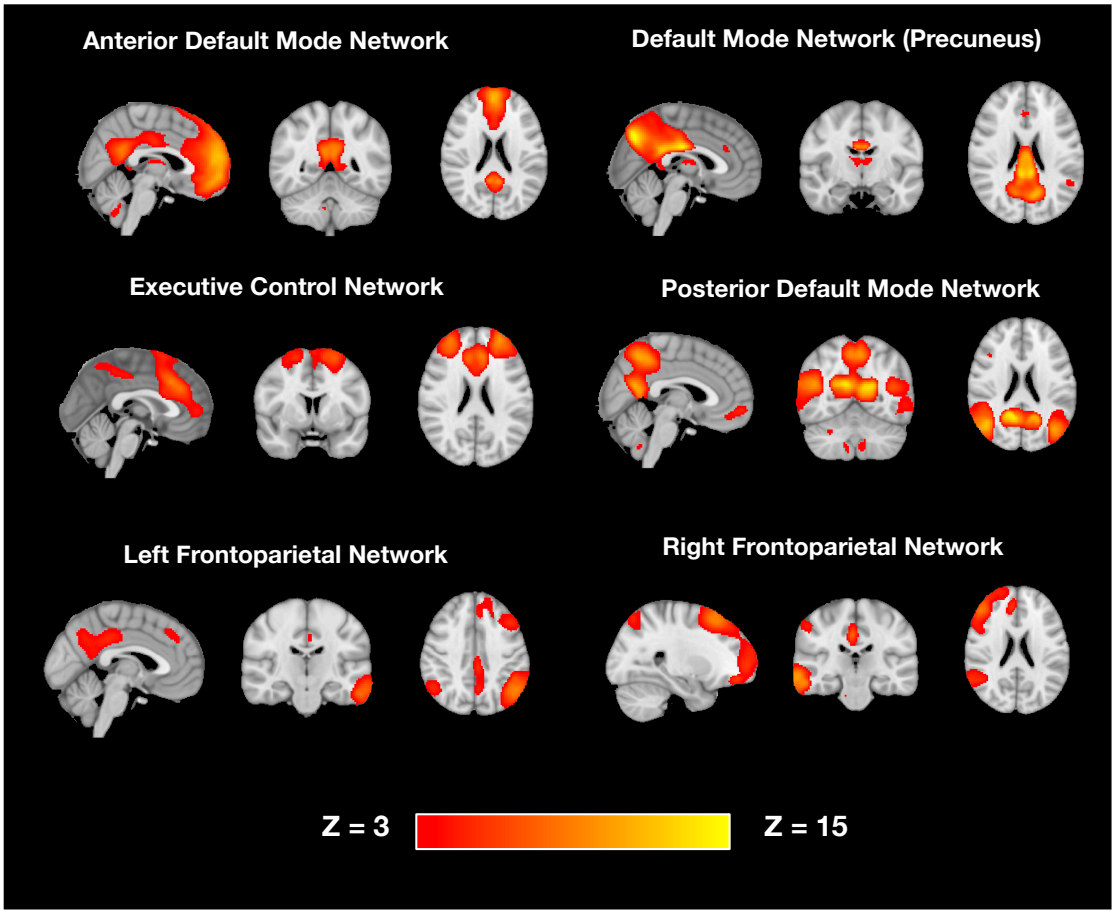
For the diffusion-weighted images, FSL's *topup* was first applied in order to estimate the susceptibility induced off-resonance field using the b0 scans (Andersson et al., 2003). Eddy was then used to correct for distortions attributed to motion and eddy currents (Andersson and Sotiropoulos, 2016). If a given slice was >3 standard deviations from the Gaussian process predicted slice these were labelled as outliers and replaced. Volumes with >10 'outlier' slices were excluded. Participants with more than 5 volumes missing from their scans were excluded from the analysis. Diffusion-weighted scans were subsequently submitted to DTIFIT, which uses a diffusion tensor model to derive spatial maps of fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD) and radial diffusivity (RD) for each individual. After this step, the Tract-Based Spatial Statistics (TBSS; Smith et al., 2006) pipeline was employed in the pre-processing of images and analysis of WM microstructure. The images produced by DTIFIT were first brain extracted with FSL's Brain Extraction Tool (Smith, 2002). Each individual's FA, AD, RD and MD images was then non-linearly registered into standard MNI space using FMRIB58_FA as the target image. They were then averaged together to make a FA skeleton which was intensity thresholded (= 0.2), in order to represent shared tracts across the entire sample. Subsequently, FA AD, RD and MD values were projected onto a study- specific mean FA tract skeleton, to derive skeletons for every participant.. Subsequently, FA AD, RD and

MD values were projected onto a study-specific mean FA tract skeleton, to derive skeletons for every participant. The averaged skeletons were intensity thresholded (= 0.2), in order to represent shared tracts across the entire sample. Mean FA, AD, RD and MD was also calculated for each participant, by averaging over these values across the entire WM skeleton. We extracted WM lesions (WML) using the automatic segmentation tool known as Brain Intensity AbNormality Classification Algorithm (BIANCA, Griffanti et al., 2016). All WML segmentations were visually inspected, excluding those that were identified as inaccurate.

Resting-state functional MRI (fMRI) images underwent the following pre-processing steps: motion correction, brain extraction, high-pass temporal filtering (cut-off = 100 sec), field map corrections; performed using FSL Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC; Beckmann et al., 2005). Artefactual components attributed to non-neuronal fluctuations were removed with single-subject ICA and FMRIB's ICA-based X-noiseifier (FIX; Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). The training data for FIX were from the WhII_MB6.RData trained-weights file (available at http://www.fmrib.ox.ac.uk/datasets/FIX-training/), consisting of manually labelled data from 25 participants. After pre-processing and cleaning, all resting-state images were registered to the individual's structural scan and standard space images using FNIRT. The images were then spatially smoothed using an isotropic Gaussian kernel of 6 mm full width at half maximum (FWHM). In order to create group-level spatial maps, MELODIC group-ICA was performed with 25 components. These spatial maps were created from all Whitehall II imaging sub-study participants with usable resting-state images and who were without any neurological diseases or structural abnormalities (n = 678). MA and Sana Suri (SS) categorised the extracted components separately as either signal or noise, with any disagreements resolved through discussion.

Dual regression (Beckmann et al., 2009; Filippini et al., 2009) was then used to extract subject-specific maps for each of the signal components in a two-stage process. Stage 1 involved using the group-average ICA spatial maps as regressors on each individual's pre-processed T_2* images, in order to extract subject-specific time-series for each ICA component. The group-average ICA spatial maps and subject-specific time-series were then used as regressors in stage 2, to extract subject-specific spatial maps of each ICA component from the pre-processed T_2* images. The images from stage 2 were then either submitted to voxel-wise analysis or used to calculate mean intra-network connectivity for each network of interest. Fslmeants was applied in the calculation of mean intra-network connectivity, using a thresholded (≥ 3) and binarized mask of the spatial map for each group-average ICA components, which was applied to each individual's corresponding spatial map. A mean was then calculated based on the connectivity of each voxel (within the mask) to the timeseries of the group-averaged ICA component. For the present analyses, our components of interest were first examined (i.e. DMN, ECN and FPN; n. of components = 6, Figure 3.1). As resting-state networks outside of our networks of interest (e.g. sensorimotor, visual) have previously been shown to demonstrate age-sensitivity (Betzel et al., 2014; Chan et al., 2014), exploratory post-hoc analyses were conducted to evaluate whether these networks correlated with social and cognitive activities (n. of components = 10, Appendix 3.4).

Figure 3.1 ICA spatial maps for components representing the ECN, DMN and FPN, overlaid on an MNI152 standard template of the brain.



3.2.7 Statistical Analyses

3.2.7.1 Comparisons of Included and Excluded Participants

To examine whether there were systematic differences between individuals included in the analysis relative to those excluded, several sociodemographic and cognitive variables were compared between groups. This included age, sex, marital status, retirement status and MoCA scores. Independent t-tests of chi-squared tests were performed, depending on the nature of the variables assessed (i.e. continuous/ categorical).

3.2.7.2 Main Analysis

FSL-VBM (Douaud et al., 2007) was used to examine whether leisure activities significantly correlated with voxel-wise measures of GM volume. Tract based spatial statistics (TBSS)

was conducted to assess the relationship between activity levels and WM integrity (i.e. FA, AD, MD, RD). Functional connectivity was examined using Dual Regression (Beckmann et al., 2009; Filippini et al., 2009). Associations for all voxel-wise analyses were assessed using FSL's randomise (Winkler et al., 2014) tool for nonparametric permutation inference (5000 permutations). Threshold-free cluster enhancement (TFCE; Smith and Nichols, 2009) was used for thresholding and a p-value of < 0.05 (Family-wise error (FWER)) corrected for multiple comparisons across space) was considered significant.

Linear regression models in SPSS (version 25) were employed to evaluate whether there was a significant relationship between leisure activity levels and cognitive function. To ensure that the assumptions of these parametric approaches were fulfilled, the correlations between predictors were checked to detect and address cases of multicollinearity (defined as Pearson's $r > 0.8$) and the distribution of model residuals were checked for normality. In the case of multicollinearity, one of the offending predictors was removed. If the error residuals of a model were highly skewed, then the dependent variable (e.g. WM lesions) was log-transformed to meet model assumptions. To reduce our number of multiple comparisons, we combined scores from the Whitehall cognitive battery to create composite measure of executive function, memory and processing speed (as done in Demnitz et al., 2017; Sexton et al., 2017). Tests where larger values reflected poorer performance (e.g. as with the TMT A) were also reverse coded (*-1). All scores were then z-score transformed, before being summed together. Linear regression models were also used to evaluate whether leisure activities significantly correlated with global GM and WM volume, WM lesions, WM microstructure (Global FA, AD, MD, RD) and average intra-network functional connectivity (FC) of the DMN, ECN and FPN. For these set of models, we report the unstandardized beta estimates (B), standard errors (SE),

standardized beta estimates (β) and p-values, with a two-tailed p-value of < 0.05 considered statistically significant.

In both the analyses of cognition and MRI measures, co-variates were selected based on prior research and entered in a step-wise manner. *Model 1* was adjusted for sociodemographic and imaging variables, including age (e.g. Ferreira and Busatto, 2013), sex (e.g. Ritchie et al., 2018), educational level (e.g. Arenaza-Urquijo et al., 2013), marital status (e.g. Shankar et al., 2013), retirement status (e.g. Xue et al., 2018), scanner model and head motion (e.g. Madan, 2018). The last two co-variates were not included in the analysis of cognitive function. *Model 2* integrated additional health and lifestyle co-variates consisting of BMI (e.g. Hamer and Batty, 2019), BP (e.g. Zonneveld et al., 2019), depressive symptoms (e.g. Dotson et al., 2009), sleep quality (e.g. Sexton et al., 2017), physical activity (e.g. Halloway et al., 2018), weekly units of alcohol consumed (e.g. Topiwala et al., 2017) and mutual adjustments between social and cognitive activities. As done in previous studies (e.g. Suri et al., 2017), total grey matter volume was additionally adjusted for in the analysis of resting-state networks. As there was one individual with missing data on one of these additional co-variates (CES-D or BMI), mean imputation was used in order to retain this individual in the analyses. Although mean imputation is known to reduce the variability in the sample (Barzi and Woodward, 2004), we did not find any substantial differences in the variances of these variables before and after adding these imputed scores.

3.3 Results

3.3.1 Sample Characteristics

Table 3.1 presents the descriptive statistics for the analytical sample (n = 624). In brief, participants were healthy older adults (mean age ± SD = 69.52 ± 5 years), with 18.6% of the sample (n = 116) identifying as female. The mean MoCA score (27.31 ± 2.19) of the

sample was within a healthy range (i.e. 26 - 30). The activities that participants spent the most time doing were reading (mean hours spent per week = 5.87 ± 3.34 hours), using the computer for leisure (mean hours spent per week = 5.87 hours ± 3.67) and visiting friends and family (mean hours spent per week = 4.17 hours ± 3.16).

Table 3.1 Participant characteristics.

		Range
N. of participants	624	
Demographics		
Age at MRI scan (years)	69.52 ± 5	60.56 – 84.58
N. of females (%)	116 (18.6)	
Educational level	3.53 ± 1.07	1 – 5
N. of individuals with partners (%)	489 (78.4)	
N. of retired individuals (%)	516 (82.7)	
Activities		
Social activity levels* (hours/ week)	11.39 ± 7.32	0 – 36.25
Cognitive activity levels* (hours/ week)	24.3 ± 9.9	0 – 60.25
Physical activity levels* (hours/ week)	14.93 ± 9.16	1 – 61.75
Health and Lifestyle		
BMI (kg/m^2)	26.07 ± 4.14	14.29 – 42.45
Blood pressure (MAP)	98.43 ± 11.61	62.33 – 146.67
Alcohol (units/ week)	14.91 ±14.47	0 – 75
Depressive symptoms (CESD score)	5.18 ± 6.12	0 –39
Sleep quality (PSQI score)	4.88 ± 2.97	0 – 17
Scanner		
% of participants scanned on Siemens Verio scanner	435 (69.7)	
Relative head motion	0.168 ± 0.89	0.01 – 0.6
Global cognition		
MoCA score	27.31 ± 2.19	18 – 30
Executive function		
Digit span forward	11.13 ± 2.28	5 – 16
Digit span backward	9.73 ± 2.47	4 – 16
Digit span sequence	10.09 ± 2.47	0 – 16
Category fluency	22.56 ± 5.4	7 – 40
Letter fluency	15.85 ± 4.48	3 – 31
TMT (B, sec)§	65.12 ± 31.74	24 – 321
Memory		
HVLT-R, Total recall	27.81 ± 4.48	11 – 36
HVLT-R, Delayed recall	9.43 ± 2.46	0 – 12
HVLT-R, RDI	10.84 ± 1.38	5 – 12
RCF, Immediate recall	16.13 ± 6.5	0 – 33

RCF, Delayed recall	15.78 ± 6.16	0 – 31
RCF, Recognition	8.56 ± 1.89	1 – 12
Processing speed		
Digit coding	63.51 ± 13.04	24 – 114
Simple (Reaction time, msec)§	314.65 ± 69.59	216.76 – 837.31
Choice (Reaction time, msec)§	341.75 ± 51.18	244.33 – 586.20
Simple (Movement time, msec)§	274.49 ± 83.66	139.93 – 681.13
Choice (Movement time, msec)§	291.02 ± 76.44	122.79 – 637.12
TMT (A, sec)§	30.35 ± 10.56	13 – 92
Structural MRI measures		
GM volume (% ICV)	38.4 ± 1.92	29.20 – 44.49
WM volume (% ICV)	37.86 ± 2.35	31.82 – 44.09
CSF (% ICV)	23.74 ± 3.14	16.45 – 35.02
WM hyperintensities (% ICV)	0.44 ± 0.25	0.08 – 2.17
FA	0.48 ± 0.02	0.41 – 0.54
AD ($x10^3$)	1.08 ± 0.02	1.01 – 1.19
MD ($x10^3$)	0.68 ± 0.03	0.61 – 0.80
RD ($x10^3$)	0.49 ± 0.03	0.40 – 0.61
Functional MRI measures#		
Anterior DMN	18.72 ± 5.73	6.00 – 44.59
DMN (Precuneus)	16.7 ± 5.37	4.77 – 36.70
Posterior DMN	13.29 ± 3.51	3.56 – 24.38
ECN	12.34 ± 4.06	4.44 – 35.07
Left FPN	17.81 ± 5.01	7.19 – 35.17
Right FPN	16.8 ± 4.27	6.19 – 35.93

Abbreviations - AD = Axial diffusivity; BMI = Body mass index; CES-D = Centre for Epidemiological Studies Depression Scale; CSF = Cerebrospinal fluid; DMN = Default mode network; FA = Fractional anisotropy; FPN = Fronto-parietal network; GM = Grey matter; HVLT-R = Hopkins Verbal Learning Test Revised; ICV = Intracranial volume; MAP = Mean arterial pressure; MD = Mean diffusivity; MoCA = Montreal Cognitive Assessment; MRI = Magnetic resonance imaging; N = number; PSQI = Pittsburgh Sleep Quality Index; RCF = Rey-Osterrieth Complex Figure; RD = Radial diffusivity; RDI = Recognition discrimination index; TMT = Trail making test; WM = White matter.
Note: Values are Mean ± Standard deviation.
For education, the scale was as follows: (1) no qualifications, (2) O-levels or equivalent (at 16 years), (3) A-levels, college certificate or professional qualification (at 18+ years), (4) degree (BSc, BA), (5) higher degree (MA, MSc, PhD).
* Un-weighted duration scores are presented, for reporting purposes.
§Raw values are reported, although scores were reverse coded for the analyses.
#measures are intra-network connectivity.

3.3.2 Comparison of Included and Excluded Participants

Individuals included in the analysis were, on average, younger ($p = 0.001$), more educated ($p = 0.04$) and scored higher on the MoCA ($p = 0.001$). While a greater percentage of the included individuals were married ($p < 0.001$), there were no differences in the percentage

of females ($p > 0.05$) or retirees ($p > 0.05$) between included and excluded participants. See Appendix 3.5 for further details on these analyses.

3.3.2 Activities and Cognitive Function

Table 3.2 provides an overview of the linear regressions performed, including for cognitive functions. Adjusting for demographic and imaging co-variates, we found a significant and positive relationship between current levels of cognitive activities and global cognition (Model 1: $B = 0.016$, $SE = 0.005$, $\beta = 0.122$, $p = 0.002$) and executive function ($B = 0.020$, $SE = 0.009$, $\beta = 0.087$, $p = 0.021$). The relationship between cognitive activities and these two cognitive measures remained significant, even after further adjustments for health and lifestyle co-variates were made (Model 2: global cognition: $p < 0.001$, executive function: $p = 0.005$). Social activities, on the other hand, were related to neither global nor domain-specific cognition (p's > 0.05).

3.3.3 Activities and Grey Matter

In models adjusting for demographic and imaging variables (Model 1, Table 3.2) cognitive activities ($B = 0.008$ $SE = 0.004$, $\beta = 0.069$, $p = 0.043$) and social activities were both associated with total GM volume ($B = 0.014$, $SE = 0.005$, $\beta = 0.096$, $p = 0.005$). Only the association between social activities and total GM volume was detected after further adjustments for lifestyle and health variables (Model 2: $p = 0.006$, Table 3.2). When it came to voxel-wise associations, a positive association was detected between social activities and a small cluster of GM localized to the right Heschl's gyrus and posterior part of the right insular cortex (102 voxels, $p = 0.037$, Table 3.3, Figure 3.2). This association was no longer significant after additional co-variate adjustments were made ($p > 0.05$). No associations were found between cognitive activities and voxel-wise indices of regional GM volume ($p > 0.05$)

Table 3.2 A summary of the linear regression results. The results for the measures of cognition, structural and resting-state functional MRI measures are reported as unstandardized beta estimates (B), standard errors (SE), standardized beta estimates (β) and p-values. All results are adjusted for age, sex, education, retirement status and marital status (Model 1). Scanner model and head motion were used as additional co-variates in the analysis of structural and resting-state MRI. For significant associations, the analyses were repeated with adjustments for BMI, BP, depressive symptoms, sleep quality, physical activity, units of alcohol and mutual adjustments between social and cognitive activities (Model 2). Total grey matter volume was additionally adjusted for in Model 2 for the analysis of intra-network functional connectivity.

Dependent Variable		**Model 1 – sociodemographic co-variates**				**Model 2 - lifestyle and health co-variates**			
	Predictors	**B**	**SE**	**β**	**p-value**	**B**	**SE**	**β**	**p-value**
Cognitive function									
Global cognition	**CA**	**0.016**	**0.005**	**0.122**	**0.002**	**0.029**	**0.007**	**0.223**	**0.000**
	SA	0.003	0.007	0.020	0.606				
Executive function	**CA**	**0.020**	**0.009**	**0.087**	**0.021**	**0.031**	**0.011**	**0.135**	**0.005**
	SA	0.013	0.011	0.044	0.235				
Memory	CA	0.074	0.039	0.072	0.063				
	SA	-0.022	0.050	-0.017	0.657				
Processing speed	CA	0.003	0.008	0.014	0.728				
	SA	-0.011	0.010	-0.045	0.259				
Brain structure									
Global GM volume (% of ICV)	**CA**	**0.008**	**0.004**	**0.069**	**0.043**	0.002	0.005	0.020	0.656
	SA	**0.014**	**0.005**	**0.096**	**0.005**	**0.014**	**0.005**	**0.095**	**0.006**
Global WM volume (% of ICV)	CA	0.000	0.004	0.002	0.945				
	SA	-0.004	0.005	-0.022	0.419				
Global WM lesions (% of ICV)[a]	CA	-0.001	0.000	-0.042	0.250				
	SA	-0.001	0.001	-0.049	0.176				
Left hippocampus (% of ICV)	CA	8.991E-05	0.000	0.042	0.266				
	SA	9.612E-05	0.000	0.035	0.348				
Right hippocampus (% of ICV)	CA	4.998E-05	0.000	0.026	0.501				
	SA	7.037E-06	0.000	0.003	0.940				
FA	CA	-3.206E-05	0.000	-0.030	0.411				
	SA	-1.695E-05	0.000	-0.012	0.732				
AD ($x10^3$)	CA	6.020E-05	0.000	0.043	0.252				

	SA	3.452E-05	0.000	0.019	0.605				
RD (x10^3)	CA	5.311E-05	0.000	0.033	0.360				
	SA	2.497E-05	0.000	0.012	0.734				
MD (x10^3)	CA	6.109E-05	0.000	0.041	0.387				
	SA	2.815E-05	0.000	0.015	0.682				
Resting-state functional connectivity*									
Anterior DMN	CA	-0.024	0.013	-0.069	0.062				
	SA	-0.022	0.016	-0.049	0.180				
DMN (Precuneus)	CA	-0.009	0.012	-0.027	0.471				
	SA	**-0.030**	**0.015**	**-0.073**	**0.049**	0.001	0.022	0.003	0.951
Posterior DMN	CA	-0.008	0.008	-0.037	0.353				
	SA	-0.015	0.010	-0.055	0.159				
Left FPN	CA	-0.004	0.011	-0.014	0.713				
	SA	0.004	0.014	0.011	0.770				
Right FPN	CA	-0.003	0.010	-0.013	0.736				
	SA	-0.007	0.013	-0.022	0.570				
ECN	CA	-0.010	0.009	-0.042	0.260				
	SA	-0.014	0.011	-0.044	0.238				

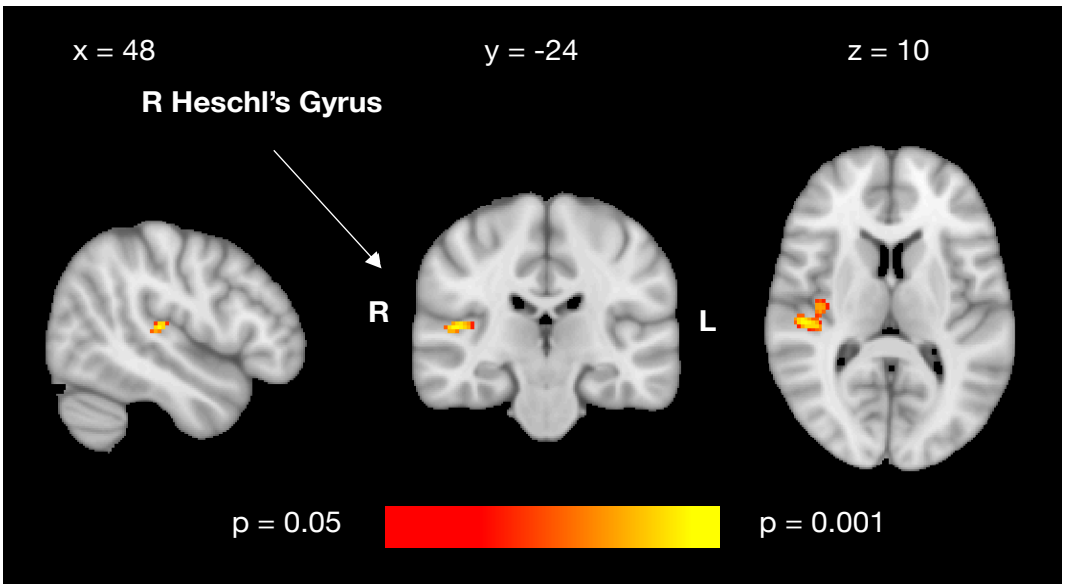
Abbreviations- AD = Axial Diffusivity; CA =Cognitive Activity; ECN = Executive Control Network; DMN = Default Mode Network; FA = Fractional Anisotropy; FPN = Frontoparietal Network; GM = Grey Matter; HVLT-R = Hopkins Verbal Learning Test- Revised; MD = Medial Diffusivity; MoCA = Montreal Cognitive Assessment; RCF = Rey-Osterrieth Complex Figure; RD = Radial Diffusivity; RDI = Recognition Discrimination Index; ; SA = Social Activity; TMT = Trail Making Test; WM = White Matter.
[a]Log-transformed due to skewed variable.
*Outcomes are intra-network connectivity.
Bold = $p < 0.05$.

Table 3.3 Coordinates of the cluster that positively correlated with social activity levels in the voxel-wise analyses of GM volume. The coordinates are presented in MNI space and the Harvard-Oxford Structural Atlas (FSLeyes tool) was used to identify the brain regions associated with the significant clusters.

Cluster N.	N of voxels	p-value	MNI coordinates of max voxel			Region
			x	y	z	
1	102	0.037	48	-24	10	R Heschl's gyrus

Abbreviations- GM = Grey Matter; MNI = Montreal Neurological Institute; N = Number; R = Right.

Figure 3.2 VBM results. Red-yellow clusters overlaid on a MNI152 standard template represent areas of GM volume that significantly and positively correlated with social activity levels, at a $p < 0.05$ (corrected for multiple comparisons across voxels and adjusted for age, sex, educational level, retirement status, marital status and scanner model).



3.3.4 Activities and White Matter

There were no significant associations between activity levels and global FA, AD, MD and RD or with global measures of WM volume ($p > 0.05$, Table 3.2). Similarly, no associations were found at a voxel-wise level.

3.3.5 Activities and resting-state functional connectivity

Intra-network connectivity of the DMN (involving the precuneus) decreased as *social activity levels* increased (B = -0.030 SE = 0.015, β = -0.073, p = 0.049), although this association did not survive further adjustments (p > 0.05, Table 3.2). No associations between cognitive activities or social activities and voxel-wise measures of DMN, ECN or FPN connectivity were found (p's > 0.05).

Post-hoc analyses indicated that *cognitive activities* were negatively linked to intra-network connectivity of the temporo-parietal network (Model 1: B = -0.016, SE = 0.008, β = -0.078, p = 0.046; Appendix 3.6), although this became non-significant after accounting for the effects of additional co-variates (Model 2: p > 0.05). Additionally, post-hoc voxel-wise analyses suggested that there was greater functional connectivity between the auditory network and two small clusters within the lingual gyrus (Cluster 1: n. of voxels = 21, MNI coordinates: x = -22, -60, -6, p = 0.029; Cluster 2: n. of voxels = 10, MNI coordinates = -12, y = -56, z = -6, p = 0.035; Appendix 3.7). Although this was no longer detected in the fully adjusted model (p > 0.05).

3.4 Discussion

In a sample of 624 British community-dwelling older adults, late-life levels of *cognitive activity* positively correlated with global cognition and executive function. Interestingly, no associations were found between cognitive activities and measures of GM volume, WM microstructure, WM lesions and resting-state functional connectivity of the ECN, DMN or FPN. On the other hand, *social activities* solely correlated with total GM volume, but did not demonstrate any associations with either overall or domain-specific cognition. We discuss the results for each activity, in turn.

3.4.1 Cognitive Activities

In 2016, a now seminal meta-analysis (Yates et al., 2016) established extensive links between intellectually stimulating activities and global- and domain-specific cognition (i.e. executive function, memory, processing speed). Our study partially replicates this pattern of results, finding that late-life cognitive activity levels associated with measures of global cognition (i.e. MoCA scores) and executive function abilities. However, unlike the meta-analysis, no associations with processing speed or memory were found. Differences in study characteristics may underlie the absence of associations with processing speed or memory. For instance, while our study utilized a cross-sectional design, 17 of the 19 studies included in the meta-analysis (Yates et al., 2016) were longitudinal, which may have been more sensitive to activity-cognition associations. Nevertheless, our study lends support to the 'use-dependency' theory, which posits that participating in cognitive activities across the lifespan and well into old age contribute to maintaining cognitive health (e.g. Hertzog et al., 2009; Salthouse, 2006).

While the reported cognitive activity-cognition associations are consistent with a large body of evidence, their directionality has been widely debated. For instance, Gow and colleagues (2012) have found associations between late-life leisure activities and cognitive function to be diminished after controlling for cognitive scores at the age of 50. Parallel observations have also been reported in an independent sample once adjustments were made for childhood IQ (Gow et al., 2012b). Yet, more recent investigations by the same research group (Gow et al., 2017) identified unique association between *mid-life* activities and cognitive function even after including prior cognitive ability as a covariate. Cross-lagged approaches applied to longitudinal data can help to tease apart the directionality of these associations of interest. As an example, one prospective cohort study of 1,076 older adults (Wilson et al., 2012) reported that activities in old age predicted better global cognition, perceptual speed, episodic and semantic memory at follow-up, while cognition did not predict subsequent activity levels. Working memory, on the other hand, had significant associations with cognition in a bi-directional manner (Wilson et al., 2012).

Other studies are however in disagreement, suggesting that baseline cognition predicts cognitive activity levels, but not vice versa (e.g. Mousavi-Nasab et al., 2014). A third line of evidence can further inform us as to whether the reported associations may form part of a causal pathway between activities and cognition. Indeed, there is a breadth of literature investigating CT generally reporting small improvements in the cognitive abilities of older adults (Mewborn et al., 2017). Yet whether these effects are only observed for trained tasks, measures related to the trained tasks (near-transfer effects), or also extends to assessments of other domains (far-transfer) remains a contentious issue (Sala et al., 2019). Overall, we encourage future authors (a) to consider using SEM based approaches (e.g. cross-lagged models) to clarify how *late life* activity participation interacts with cognitive ageing and (b) to investigate whether these translate to general or specific *effects* using RCT methodology.

Despite the reported links between cognitive activities and cognition, the present study found that these activities did not have a unique association with whole-brain GM volume, after adjusting for sociodemographic and imaging co-variates. No associations were detected for regional GM volume in our voxel-wise analysis, either. Our study is in line with prior evidence that has also reported null findings between late-life levels of cognitive activities and GM volume (Foubert-Samier et al., 2012; Gidicsin et al., 2015; Schultz et al., 2015), although, are less consistent with a VBM study (Arenaza-Urquijo et al., 2016) and region-of-interest study (Seider et al., 2016) that contrastingly report widespread associations between cognitive activities and GM. Similarly, no associations with any of the DTI metrics, or total WM lesions were identified. Previous studies have also failed to find any associations between cognitive activities and FA (Gow et al., 2012a; Köhncke et al., 2016), MD (Köhncke et al., 2016) or WM lesions (Gow et al., 2012a; Köhncke et al., 2016). As in the case of GM outcomes, some studies contest our findings (e.g Arfanakis et al., 2016), with the results of Chapter 2 (on global WM lesions) also challenging the results presented here. Our study was also the first to comprehensively evaluate whether cognitive activities relate to resting-state functional connectivity. While we initially identified positive links between cognitive activity participation and connectivity of auditory network (a post-hoc network), these small associations were no longer detected after further co-variate adjustments were made. Taken together, these results indicate that the null findings reported for structural MRI may also extend to this modality. Overall, the inconsistencies between our results and prior findings may be down to inter-study differences in the activities used to define our constructs of interest, i.e. cognitive/social activities.

A key question that arises from the present chapter is why we observed associations between cognitive activities and cognition, but not with MRI markers of structural or

functional integrity. One likely explanation is that our cognitive outcomes, which involved creating a composite measure based on scores from independent but related tests, were more sensitive to detecting these hypothesized associations relative to voxel-wise approaches. While the latter approach involves pooling together effect sizes, the voxel-wise analyses instead add an extra 'layer' of corrections in order to minimize the Type I error rate. These multiple comparisons corrections may have contributed to an underpowered analysis, particularly if the effects of interest are small. Another potential reason is that our cross-sectional design makes it impossible for us to differentiate between individuals who recently took up an intensive regime of activities (post-retirement) relative to individuals who have been consistently intellectually engaged over their lifespan. We later argue that the activity habits of the latter group may be more likely to have detectable changes in their brain structure/functional connectivity, with the discussion expanded upon in the *Strengths and Limitations* section of this chapter. Finally, longitudinal MRI (e.g. Köhncke et al., 2016) or other MRI modalities (e.g. PET imaging; Arenaza-Urquijo et al., 2015) could have improved our ability to detect the neural mechanisms that may underlie the cognitive activity-cognition associations. Our selection of modalities was, however, informed by prior studies and it would be important for a future large-scale study, using the same method of defining cognitive/social activities and examining similar MRI modalities, to evaluate whether our findings are replicable.

3.4.2 Social Activities

Contrary to our hypotheses, we did not find social activities to associate with either global or domain-specific cognition. These results were surprising, particularly as a recent meta-analysis published in the field suggests otherwise. The review, conducted by Evans et al. (2018) reported that after pooling the data from 39 longitudinal cohort studies, regularly participating in social activities was systematically related to greater measures of global

cognition, memory and executive function (processing speed was not examined). Notably, the reported pooled effect sizes were small, despite there being a large number of participants included in each meta-analysis: global cognition (n = 51,804; Pearson's r = 0.072), executive function (n = 24,494; Pearson's r = 0.032), memory (n = 29,099; Pearson's r = 0.049; Evans et al., 2018). Interestingly, the strength of the associations also weakened for studies with shorter follow-ups, which has clear implications for our cross-sectional study of < 700 participants and may explain the absence of any links with cognition. Given that a meta-analysis of such a large dataset only detected small effects, however, raises the question of whether social engagement explains a sufficient amount of variance in cognitive function to be clinically of interest (Miller et al., 2016). For example, socially demanding activities only appeared to account for 0.24% of the variance in memory (Kirk, 1996) in the previously mentioned review. Yet differences between study designs may in part underlie the small effects (Evans et al., 2018), with one potential source of heterogeneity being the variety of measures used to assess cognition.

Another consideration is that our approach combined multiple cognitive tests to create composite measures, which may have attenuated effects of independent measures. With this in mind, a series of post-hoc analyses were performed to see whether there was evidence to support this explanation (Appendix 3.8). The post-hoc results were consistent in providing *no support* that social activities associated with performance on any of the 18 tests after adjusting for sociodemographic, imaging, health and lifestyle factors ($p > 0.05$). These results call into question whether improving social activity participation in older adults will have a *clinically meaningful* effect on cognition. For example, one study of Chinese older adults found improvements only in category fluency after a 40 week intensive community-based social intervention (1-hour meetings held three times a week; Mortimer et al., 2012). That being said, it may be the case that *long-term* exposure to a socially

stimulating environment has a more substantial role in supporting late life cognitive function. Longitudinal studies will be more appropriate to test the hypothesis that life-long, versus, recent increases in social engagement are more strongly related to cognitive function in later life.

Contrary to the null findings in Chapter 2, greater social engagement was found to independently relate to greater global volumetric measures of global GM volume. Inter-study heterogeneity could be drawn upon once more to explain the discordant findings with our meta-analysis, as flagged by a significant I^2 statistic suggesting that 67.1% of the effect size variance in the meta-analysis of GM volume was attributable to between study differences. Our voxel-wise analyses further suggested that higher social activity levels were significantly associated with greater GM volume, within two small clusters localized to the right Heschl's gyrus and insular cortex. This cluster was, however, no longer detected once lifestyle and health variables (including cognitive activities) were included as confounders. An absence of associations has previously been reported by Foubert-Samier and colleagues (2012), although this is in disagreement with a study published in the same year (James et al., 2012), who identified activity-sensitive clusters localized to the temporal lobe even after following adjusting for a range of demographic and health covariates. Neither study, however, controlled for the effects of cognitive activities. As individuals who are intellectually active tend to dedicate more time to social commitments (Pearson's $r = 0.616$,) cognitive activities may act as a confounding variable in the relationship between social activities and regional GM volume. Our results therefore emphasize the importance of taking mutual activity effects into account in future studies.

It was interesting to find that while social activity-local GM associations were no longer significant, the relationship with whole-brain GM volume persisted. James et al. (2012) has also previously reported a link between social activities and global GM volume, with

consistently small effect sizes reported in both the previous (β = 0.072), and the current study (β = 0.095). No other associations with brain structure, including WM microstructure, WM volume and WM lesions were found, a pattern of results that has previously been observed (Bennett et al., 2006; James et al., 2012; Vaughan et al., 2014). When it came to resting-state functional connectivity, social activities were initially linked to intra-network connectivity of the anterior DMN, although this association also disappeared after further confounders were taken into account. While there are no known fMRI studies that have specifically examined social activity levels in older adults, a related construct - *social network size* - has gained comparatively more attention from neuroimaging studies (Bang et al., 2019; Pillemer et al., 2017). Summarizing the results of Pillemer and colleagues (2017), their study reported that larger social networks correlated with higher intra-network connectivity of the sensorimotor, visual, vestibular, insular and left frontoparietal functional brain networks in a sample of community dwelling older adults. It should be noted, however, that none of the 4 ICA components classified as signal (Total n. of components = 20) corresponded to whole DMN in this study, which may have been down to noisy data acquired in a small dataset (*N.* of participants = 28; Pillemer et al., 2017). In the present study, we did not find any associations with intra-network connectivity, even when examining other age-sensitive networks (e.g. sensorimotor and visual networks, Appendix 3.6). This could be taken to suggest that the associations reported in Pillemer et al. (2017) are specific to the size of an individual's network, and do not extend to other dimensions of social engagement (i.e. participation in social activities). To thoroughly test this conclusion, a future study of interest may be conducted to compare how different markers of social engagement (e.g. network size, living circumstances, marital status, social activity levels) differentially relate to resting-state functional connectivity. This avenue will help clarify the extent to which social enrichment contributes to maintaining the ageing brain.

3.5 Strengths and Limitations

One of the major strengths of this study is that multi-modal MRI was used to investigate how late life levels of activities relate to the ageing brain. Furthermore, this study also focused on a large and well characterized sample of older adults. Given the limitation of the 'mutually exclusive' approach (i.e. either cognitive or social activities) in defining activities (detailed in Chapter 2), we used a more 'real-world' approach that allowed a given activity to feature in both composite measures, provided that they were rated as both socially *and* cognitively demanding. Although the cross-sectional methodology of our study is useful in understanding whether *current* (i.e. late life) participation in activities was linked to markers of brain ageing, it conversely prevents any inferences regarding the directionality of these associations. Certainly, it may be the case that these results are primarily driven by individuals in the prodromal stages of disease withdrawing from everyday activities that become too challenging for them to do. Comparisons between excluded and included participants further suggested that our sample might represent a healthier/more able group of older adults, as they appeared to be younger, more educated and scored higher on the MoCA compared to excluded individuals. A biased sample may further explain the lack of significant associations reported here, for instance, due to insufficient sample variability.

Another consequence of the cross-sectional nature of the analyses described here is that it only provides a mere 'snapshot' into the nature of the associations investigated. In other words, they fail to give any insight into *past* activity habits, meaning it was not possible to differentiate between individuals *consistently active* over their lifetime and those who had become *recently active* as a consequence of, e.g. retirement. Based on the rationale that *sustained* engagement in leisure activities is more likely to contribute to brain health in old age (Bartrés-Faz and Arenaza-Urquijo, 2011), we posit that maintaining high levels of

participation, compared to recent increases in activity levels, might harbour stronger associations with structural and resting-state MRI markers. Indeed, lifetime social and cognitive activities levels have previously been linked to less age-related volumetric loss of the hippocampus (Valenzuela et al., 2008) and greater GM volume in frontal and parietal regions (Bartrés-Faz et al., 2009), although null findings in relation to WM lesions have also been reported (Wirth et al., 2014). A minority of studies has examined further how activity levels within specific lifetime periods (e.g. early- and mid-life) relate to the ageing brain, with the current evidence mixed (Foubert-Samier et al., 2012; Suo et al., 2012; Valenzuela et al., 2008). As mentioned in Chapter 2, the main measurement tools employed in the field have been retrospective assessments of activities (with some questions referring to childhood habits), calling into question the validity of what is remembered and reported (Gow et al., 2017). Overall, longitudinal studies with repeat activity measures are urgently needed.

3.6 Conclusion

In conclusion, the results of the present chapter indicate that the associations between current levels of leisure activities, brain structure and functional connectivity are sparse. Social activity was the only one of the activities to independently link with global GM volume but did not correlate with any of the indices of cognitive function. Cognitive activities, on the other hand, correlated with both global cognition and executive function, but demonstrated no associations with any of the MRI indices. One of the key points discussed here is that prior activity habits could be an important factor to take into account when assessing activity-brain associations. Overall, we encourage other authors in the field to move away from oft-used cross-sectional methodologies towards longitudinal investigations, to collaboratively progress towards better characterizing the links between activities and the ageing brain.

CHAPTER 4

Trajectories of Activity Levels Between Mid- and Late Life and Their Relationship to Brain Integrity in the Whitehall II Cohort

Contents

Abstract 120

4.1 Introduction 122

4.2 Methods 124

4.3 Results 132

4.4 Discussion 142

4.5 Strengths and Limitations 148

4.5 Conclusion 150

Abstract

While Chapter 2 indicated consistent links between socio-intellectual activities and several neuroimaging metrics of brain structure, Chapter 3 only identified minimal associations when activity sub-types were evaluated independently. A caveat of the prior chapter, however, is its cross-sectional method and the focus on *current* activity habits. Chapter 4 aims to take a step further, by examining how longitudinal assessments of activities relate to the ageing brain. Specifically, this chapter revisits the Whitehall II dataset, with the aim of (1) examining how self-reported activities change between mid-life and late life and how best to model this and (2) evaluating whether activity trajectories are significantly associated with brain structure, functional connectivity and cognition. In this way, the present chapter offers one of the most detailed investigations into the relationship between activities and the brain in old age, to date.

Using data collected from 574 members of the Whitehall II study, activity levels were measured five times over a period of 15 years. A series of latent growth curve models and latent class growth models were first applied to elucidate the pattern of change in activity levels over time. Subsequently, parameters describing each individual's trajectory were derived from the best fitting model and used as regressors in a set of general linear models where GM volume, WM microstructure, functional connectivity and cognitive function were examined as dependent variables.

Our first main finding was that the quadratic latent growth curve model best described longitudinal patterns of social and cognitive activity levels in the Whitehall sample. Therefore, we derived parameters that described each individual's predicted trajectories, namely, their activity intercepts, linear and quadratic coefficients. Overall, the predicted level (i.e. intercepts) of cognitive activities positively related to global cognition, executive function, memory and processing speed. Trajectories following an initial increase and subsequent levelling off/decline in cognitive activities were linked to higher global cognition, executive function, memory and global GM volume. Social activity levels demonstrated associations with executive function only, with trajectories following a more curved shape correlating with poorer outcomes on tests of executive function. No voxel-wise assocaitions of GM, WM or the resting-state networks of interest (i.e. DMN, ECN, FPN) were identified, although post-hoc tests highlighted the sensorimotor network as a potential network of interest for future studies. Overall, this chapter demonstrates that *maintaining and increasing* levels of cognitive and social activities between mid- and late life may contribute to promoting cognitive health in old age.

Keywords: Leisure activity, cognitive ageing, Whitehall, longitudinal, trajectories, latent growth curve models, latent class growth analyses.

4.1 Introduction

One of the recurring points of discussion in this thesis has been the issue that published MRI studies have tended to rely on cross-sectional methods and retrospective assessments of activities, limiting our ability to characterize the associations between leisure activities and the ageing brain. Even the few studies that have used a longitudinal design are hindered by their shortcomings. For instance, these investigations often follow participants for a limited period of time (i.e. n of studies = 8, length of interval = 1 month – 5 years; Anatürk et al., 2018) and have typically only measured activity levels at two time points. Due to these limitations, the current evidence poorly captures the *dynamic* changes in activities that occur over an individual's lifetime (King et al., 2017).

The development of longitudinal modelling techniques, including growth curve and mixed effects models, now provide an avenue to better delineate the relationship between life-time activities and brain health. However, these methods continue to be underutilized in MRI studies (King et al., 2017) despite the need to capture both intra-individual changes and inter-individual differences. For example, middle-aged adults do not necessarily exhibit the same activity patterns over time (i.e. *intra-individual* changes). In fact, socializing habits are rarely reported as stable across the lifespan, with many studies finding that engagement in this type of activity either decreases or increases from mid-life to late life (Pinto and Neri, 2017), while cognitive activity levels have been reported largely to decline over time (Mitchell et al., 2012). With regard to *inter-individual* differences in activity levels over time, studies using hypothesis-free data-driven approaches report that there may be up to five sub-groups of adults following different social activity trajectories – identifying some as healthier than others (Park et al., 2017; Thomas, 2012, 2011). This is demonstrated by Thomas (2012), who found that individuals with high and increasing socializing habits over time had a 37% reduced risk of mortality, relative to those who had low and decreasing

social engagement levels (Thomas, 2012). Overall, these results indicate that characterising the pattern of change in activities and their links with brain structure and function could help to delineate their contribution to brain integrity in later life further, with important implications for developing interventions to promote healthy ageing.

4.1.1 Aims

To the best of our knowledge, there are no previous studies that have examined whether cognitive and social activity trajectories, measured between mid-life and late life, relate to structural and functional brain markers in old age. In the present chapter, we therefore aimed to: (1) evaluate whether there are sub-groups of individuals following similar patterns of cognitive and social activity levels over time and (2) examine how trajectories of cognitive and social engagement relate to MRI markers of brain structure, functional connectivity and cognition in old age. Based on previous findings, we hypothesized to find five sub-groups following different activity trajectories (Park et al., 2017; Thomas, 2012, 2011). We furthermore hypothesized that greater levels of, and increases in, cognitive and social activities over time are related to higher levels of global cognition, executive function, processing speed and memory, greater GM and WM volume, better WM integrity (e.g. higher FA, lower MD) and fewer WM lesions (Anatürk et al., 2018). Similar to Chapter 2, an ICA-based analysis was performed to evaluate whether activity trajectories were related to DMN, ECN and FPN connectivity. As our results suggested that there were no associations between the *level* of cognitive/social activities and connectivity of the DMN, ECN or FPN, we would expect to find that *changes* in activities may instead be linked to functional connectivity. Otherwise, no predictions regarding resting-state functional connectivity were made.

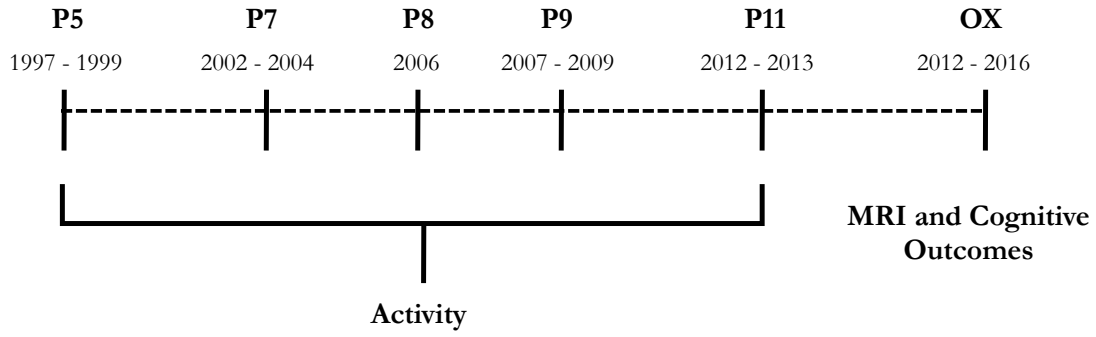
4.2 Methods

4.2.1 Sample Characteristics

Participants were members of the Whitehall II study (Marmot et al., 1991) and imaging sub-study (Filippini et al., 2014). See Chapter 2 for a description of this cohort study and its sub-study.

The current analyses are based on data related to leisure activity levels collected in five waves over 1997-1999, 2002-2004, 2006, 2007-2009 and 2011-2013, and MRI and cognitive data between 2012-2016. For an overview of the included study phases, see Figure 4.1. The study received ethical approval from the University of Oxford Medical Sciences Interdivisional Research Ethics Committee (MSD/IDREC/C1/2011/71), as well as the University College London Medical School Committee on the Ethics of Human Research (Committee Alpha, reference: 85/0938). All participants enrolled in this study gave their informed and written consent.

Figure 4.1. A timeline of the study phases and key variables included in the present analyses.



Abbreviations- MRI = Magnetic resonance imaging; OX = Oxford scanning visit; P = Phase.

4.2.2 Inclusion and exclusion criteria

The sample consisted of individuals who had completed the activity questionnaire in at least four of the five data waves and had no more than 1 item missing from each completed activity questionnaire (N of missing = 51). Other reasons for exclusion were incomplete data for the cognitive or MRI outcomes of interest (N = 25), motion or scanner artefacts present in the structural, diffusion-weighted or resting-state scans (N = 39), incidental findings on the MRI scans (e.g. large cysts, tumours, strokes, N = 23) or a self-reported a diagnosis of a neurological disorder, such as Parkinson's Disease, Stroke or Multiple Sclerosis (N = 41). For a flowchart of participant selection and exclusion, see Appendix 4.1.

4.2.3 Cognitive and Social Activity Levels

The activity items form part of the study questionnaire that was administered to all participants. Respondents were asked to indicate how frequently they had engaged in 13 activities over the past 12 months, on a 4-point scale. The activities assessed included visiting friends and family, volunteering, attending educational/evening classes, cultural visits and using a computer for leisure, with the full list of activities found in Appendix 4.2. Scores for these items were reverse-coded, so that higher scores represented more frequent participation in activities (i.e. 0 = never, 1 = rarely, 2 = monthly, 3 = weekly).

As activities vary in their cognitive and social requirements (Anatürk et al., 2018), we weighted each item by their relative demand. Item weightings are based on the assignments made in Chapter 3 by authors MA, Claire Sexton (CES), and Klaus Ebmeier (KPE; for agreed ratings, see Appendix 4.2). The weights assigned consisted of 'low' (= 0), 'medium' (= 1) or 'high' (= 2) cognitive/social demand. Hence, an item with a higher cognitive

demand weighting, for example, provided a greater contribution towards the overall cognitive engagement score compared to an activity deemed to be less demanding.

A weighted mean (Manikandan, 2011) was then calculated as follows:

$$\frac{(item_1*weight)+(item_2*weight_2)\ \ldots\ (item_n*weight_n)}{weight_1 + weight_2 + \ldots weight_n}$$

This produced two summary score (ranging from 0-3) that reflected either cognitive or social activity engagement, where higher values indicate greater levels of engagement.

4.2.4 Cognitive Function

As in Chapter 3, scores on each cognitive test were z-score transformed and summed together to produce indices of three sub-domains: *executive function* (digit span test: forward, backward and sequence (Wechsler, 2008); language fluency: category and verbal; TMT: part B), *memory* (RCF (Osterrieth, 1944): immediate recall, delayed recall and recognition; HVLT-R (Brandt, 1991): total recall, delayed recall and recognition) and *processing speed* (TMT (Reitan, 1958): part A; digit coding (Wechsler, 2008) and CANTAB RTI; CANTABeclipse 5.0; Cambridge Cognition Ltd: simple reaction time, choice reaction time, simple movement and movement time (Sahakian et al., 1993). *Global cognition* was measured using the MoCA (Nasreddine et al., 2005). For the CANTAB and TMT measures, scores were multiplied by -1 so that higher scores indicated better performance.

4.2.5 Demographic and Health Variables

Age in 1997-1999 (trajectory analyses) or age at the time of scan (neuroimaging analyses) was used as a covariate. A description of all other demographic variables examined in here is provided in section 3.2.5 of Chapter 3.

4.2.6 MRI Data Acquisition and Pre-processing

MRI data acquisition and pre-processing are detailed in Chapter 3.

4.2.7 Missing Data

Instead of excluding respondents who had omitted a single item on the activity questionnaire, we used the weighted mean score from all items available at each time point. Weighted means for each time point were used to reduce the bias introduced by the one missing item on the overall summary score.

Full Information Maximum Likelihood was employed to address situations where an entire questionnaire was missing from a participant at a particular phase (e.g. due to non-attendance on the assessment day). This method uses all available information to estimate population parameters and has previously been shown to be less biased than common deletion (i.e. pair-wise or list-wise) or mean imputation methods of handling missing data (Enders and Bandalos, 2001; Little et al., 2014; Wothke, 2000).

4.2.8 Statistical Analysis

4.2.8.1 Comparisons of Included and Excluded Participants

Independent t-tests or chi-squared tests, for continuous and categorical variables respectively, were applied to assess whether included and excluded participants differed on key demographic and cognitive variables (age, sex, education, marital status, retirement status and MoCA).

4.2.8.2 Trajectory Analyses

To examine whether Whitehall II participants could be reliably sub-divided into groups

based on their repeat measures of social and cognitive activity levels, we performed a series of latent growth curve models (LGCM; for schematic diagram see Appendix 4.3) and latent class growth models (LCGM; for schematic diagram see Appendix 4.4). LGCMs were used to estimate a single mean trajectory across all study participants, while also estimating individual variability around this mean trajectory (Curran et al., 2010). This, in effect, served as our 'null hypothesis' model, i.e. that a single group model (relative to 'multi-group' models) best explains the data (Ram and Grimm, 2009). LGCMs models are flexible when it comes to the shapes of change that they are able to represent (Andruff et al., 2009; Jung and Wickrama, 2008). In this particular study, we examined: (1) intercept-only/no change (2) linear change and (3) quadratic change over time. We assessed the fit of LGCM models based on the Akaike Information Criterion (AIC; Akaike, 1974), Bayesian Information Criterion (BIC; Schwarz, 1978), and Sample-Size Adjusted BIC (SSA-BIC; Sclove, 1987), Tucker-Lewis Index (TLI; Tucker and Lewis, 1973), Comparative Fit Index (CFI; Bentler, 1990) and Root Mean Square Error of Approximation (RMSEA; Steiger and Lind, 1980). For further details on these fit indices, see Appendix 4.5. Following Grimm et al. (2011) we considered adequate fit as a combination of the following: TLI $\geq$ 0.95, CFI $\geq$ 0.95 (Hu and Bentler, 1999) and a RMSEA $\geq$ 0.10 (MacCallum et al., 1996). AIC, BIC, and SSA-BIC were also used to compare models, with lower values indicating better fit (Grimm et al., 2011). As large sample sizes can bias the likelihood ratio chi-square towards rejecting even well-fitting models (Preacher et al., 2008), this fit index was not considered in our model comparisons.

LCGMs are a type of finite mixture modelling, used to classify individuals into sub-groups not known *a priori*, commonly referred to as 'latent classes' (Jung and Wickrama, 2008). LCGM assume that there is no variance in the intercepts or slopes (or covariance) of activity levels *within* the sub-groups identified (Twisk and Hoekstra, 2012). While growth

mixture models (GMM) are more flexible and do allow for within-class variance, these were not performed in the current study because they commonly experience model convergence issues, identify unstable classes and produce low entropy, relative to LCGMs (an index of model's classification 'confidence'; Jung and Wickrama, 2008). We assessed a variety of unconditional and conditional (adjusted for baseline age, sex, educational level) LCGMs, varying the number of sub-groups extracted (2 - 6) and shapes of change modelled (i.e. intercept-only, linear and quadratic pattern of growth). Note that we also evaluated models where the shape of change was allowed to differ between sub-groups, as done in prior publications (Andruff et al., 2009). Once all of the LCGM analyses had been run, we compared each model based on established indices of fit (Jung and Wickrama, 2008; Ram and Grimm, 2009). First, the AIC, BIC, SSA-BIC of each model were compared relative to the 'single-group' LGCMs. Models that did not show improved fit were rejected, whereas those that had better fit were compared. Among the LCGMs, the model with best fit was identified as having the lowest AIC, BIC and SSA-BIC values, entropy values ≥ 0.8 and a p-value < 0.05 for the Lo-Mendel-Rubin likelihood ratio test (LRT-RT; Lo et al., 2001) and Bootstrap likelihood ratio test (BLRT; McLachlan and Peel, 2000). An overview of these indices can be found in Appendix 4.5. A minimum of 5% of participants within each class was also considered essential for model selection (Andruff et al., 2009).

For both the LGCM and LCGM analyses, time scores were entered as the mean years since the baseline assessment (i.e. 0, 6, 9, 11 and 15 years since Phase 5), dividing by either 10 for LGCMs (Rosenberg et al., 2018) or 100 for LCGMs (Berlin et al., 2014) to aid model convergence. Restricted Maximum Likelihood with robust standard errors was also used for all models, as the estimates produced from this estimator are robust to deviations from normality (Muthén and Muthén, 2010). Variances of the observed variables (i.e. activity

measures) were constrained to be equal over time. All LGCM and LCGM analyses were conducted in MPLUS (version 8).

4.2.8.3 Neuroimaging Analyses

As the quadratic LGCM (Figures 4.2 and 4.3) was found to have the best fit for cognitive and social engagement levels over time, we extracted parameters from this model describing the predicted activity trajectories of each participant (to see plots of individual versus actual trajectories, see Appendix 4.6). These parameters consisted of the intercepts, linear slopes and quadratic slopes (herein, referred to as intercept, linear and quadratic coefficients). To reduce collinearity between the slope and quadratic growth coefficients, time scores were centred at the middle time point (Phase 8; L. Muthén 2018, personal communication, 27th July 2018). Intercepts, therefore, reflected the estimated mean at Phase 8, with slopes representing the annual rate of change at this time point (Grimm et al., 2011). The quadratic coefficients, on the other hand, remained constant over time, reflecting *change* in slope across time, otherwise interpreted as the acceleration or deceleration of change in activity levels (Grimm et al., 2011).

To evaluate whether longitudinal trajectories of activity participation relate to structural indices and functional connectivity measures, the intercepts, linear and quadratic coefficients were entered as predictors in a series of general linear models. Here, the dependent variables were voxel-wise measures of GM volume, WM microstructure and functional connectivity. Specifically, voxel-wise measures of GM volume were examined using FSL-VBM (Douaud et al., 2007). WM integrity, including FA, AD, MD and RD, was examined with TBSS (v1.2; Smith et al., 2006). Functional connectivity of DMN, ECN and FPN was evaluated using Dual Regression (Filippini et al., 2009). All voxel-wise statistics were performed with the FSL randomise (Winkler et al., 2014) tool for

nonparametric permutation inference with 5000 permutations. Threshold-Free Cluster Enhancement (TFCE; Smith and Nichols, 2009) was used for thresholding, and a two-tailed p-value < 0.05 (family-wise error corrected for multiple comparisons across space) was considered significant. In the main text, we report and discuss clusters that survived this threshold and consisted of at least 10 voxels, while clusters <10 voxels are reported in Appendices 4.12-4.13).

Linear regression models (SPSS version 25) were performed to examine whether the intercepts, linear or quadratic coefficients were related to measures of global and domain-specific (i.e. executive function, memory, processing speed) cognitive function. structural and functional indices were also examined as dependent variables, including total GM, WM and WM lesions volume (expressed as a % of ICV), WM microstructure (global FA, AD, MD, RD), and average within-network functional connectivity of the DMN, ECN and FPN. Cases of multi-collinearity (defined as a Pearson's r > 0.8) were dealt with by removing one of the involved predictors. The standardized residuals for each linear regression were visually checked to see if they were normally distributed and in the instance of skewed data, the dependent variables were log-transformed.

Model 1 was adjusted for age at the time of scan, sex, educational level, marital status, retirement status, scanner model and head motion. These confounders (apart from scanner model and head motion) were also included in the analyses of cognitive outcomes. Correlations between trajectories of cognitive and social activities indicated multicollinearity between these variables (e.g. Pearson's r between intercepts = 0.865), hence, our regression models did not include mutual adjustments between activity trajectories, as too high correlations between predictors can bias standard estimates and produce unreliable p-values (Vatcheva et al., 2016). For cognitive activities, high correlations were also detected between intercepts and quadratic coefficients (Pearson's r

= -0.855), and therefore we repeated the analyses separately for each parameter.

Associations found to be significant between activity trajectories and the outcomes of interest were subjected to a further analysis that took into account additional health and lifestyle co-variates. Model 2 was further adjusted for BMI, BP (MAP), depressive symptoms, sleep quality, units of alcohol and physical activity levels. Total GM volume (% of ICV) was also co-varied for at this stage in the analysis of resting-state networks. Prior to these analyses, there were one or two individuals with missing data on these additional co-variates (i.e. CES-D (n = 2), BP (n = 1) physical activity (n = 2). As done in Chapter 3, mean imputation was used to retain these individuals in the analysis. Given the very few imputed scores, no substantial reductions in the variance of these variables were identified pre- and post- imputation. Unstandardized beta estimates (B), standard errors (SE), standardized beta estimates (β) and p-values are reported. A two-sided p-value < 0.05 was considered significant for these regression analyses.

4.3 Results

4.3.1 Sample Characteristics

The descriptive statistics for included participants are reported in Table 4.1. Briefly, there were a total of 574 participants included in the main analyses, with a mean age of 69.6 years (SD = 4.93, range = 60.6 – 84.4) at the MRI examination (2012-2016). Females represented 18.5% of the total sample (n = 106). Overall, the mean MoCA scores within the sample was 27.4 (SD = 2.11). The most frequently undertaken activities were reading (n = 502 (87.5%) reporting weekly engagement), using the computer for leisure (n = 258 (44.9%)) and visiting family and friends (n = 220 (38.3%)).

4.3.2 Comparisons of Included and Excluded Participants

On average, participants included in the analyses were younger ($p = 0.018$), more educated ($p = 0.031$) and achieved higher MoCA scores ($p < 0.001$) relative to excluded participants. A higher proportion of included individuals were married, relative to excluded individuals ($p = 0.003$). There were no differences in the proportion of females or retirees between these groups (For results, see Appendix 4.7).

Table 4.1 Characteristics of the analytical sample.

		Range
N. of participants	574	
Duration between baseline and MRI scan	16.41	13.66 – 19.47
Demographics		
Age at baseline (years)		
Age at scan (years)	69.57 ± 4.93	60.56 – 84.35
N. of females (%)	106 (18.5%)	
Educational level	3.54 ± 1.06	1 – 5
N. of individuals with partners (%)	451 ± 78.6	
N. of retired individuals (%)	478 ± 83.3	
Activities		
Cognitive activity at baseline (weighted mean)	1.02 ± 0.35	0 – 2.35
Social activity at baseline (weighted mean)	1.04 ± 0.44	0 – 2.36
Physical activity at MRI scan (weighted hours/ week)	21. 34 ± 14.25	1 – 92.75
Health and Lifestyle		
BMI (kg/m^2)	26.03	14.29 – 42.45
Blood pressure (MAP)	98.43 ± 11.72	62.33 – 146.67
Alcohol (units/ week)	15.16 ± 14.43	0 – 75
Depressive symptoms (CES-D score)	5.11 ± 5.94	0 – 39
Sleep quality (PSQI score)	4.9 ± 3.03	0 – 17
Scanner		
% of participants scanned on Siemens Verio scanner	435 (69.7)	
Relative head motion	0.17 ± 0.09	0.01 – 0.6
Global cognition		
MoCA	27.38 ± 2.11	18 – 30
Executive function		
Digit span forward	10.15 ± 2.42	5 – 16
Digit span backward	9.77 ± 2.44	4 –16
Digit span sequence	10.15 ± 2.42	1 – 16
Category fluency	22.66 ± 5.39	1 – 16

Letter fluency	15.88 ± 4.45	3 – 31
TMT (B, sec)*	63.92 ± 29.62	24 – 289
Memory		
HVLT-R, Total recall	27.88 ± 4.41	11 – 36
HVLT-R, Delayed recall	9.49 ± 2.40	0 – 12
HVLT-R, RDI	10.85 ± 1.37	5 – 12
RCF, Immediate recall	16.26 ± 6.36	0 – 33
RCF, Delayed recall	15.92 ± 6.01	0 –31
RCF, Recognition	8.60 ± 1.87	1 –12
Processing speed		
Digit coding	63.8 ± 12.94	24 – 114
Simple (Reaction time, msec)*	314.23 ± 69.21	216.76 – 837.31
Choice (Reaction time, msec)*	340.78 ± 51.24	244.33 – 586.20
Simple (Movement time, msec)*	274.62 ± 82.89	139.93 – 681.13
Choice (Movement time, msec)*	290.87 ± 74.6	122.79 – 637.12
TMT (A, sec)*	29.98 ± 10.09	13 – 92
Structural MRI measures		
Global GM volume (% ICV)	38.37 ± 1.94	29.20 – 44.49
Global WM volume (% ICV)	37.85 ± 2.33	31.82 – 44.09
CSF (% ICV)	23.79 ± 3.11	16.45 – 35.02
Global WM hyperintensities (%ICV)		
FA	0.48 ± 0.02	0.41 – 0.54
AD ($x10^3$)	1.08 ± 0.02	1.01 – 1.19
MD ($x10^3$)	0.68 ± 0.03	0.61 – 0.80
RD ($x10^3$)	0.49 ± 0.03	0.40 – 0.61
Functional MRI measures#		
Anterior DMN	18.77 ± 5.82	5.99 – 44.58
DMN (Precuneus)	16.75 ± 5.32	4.77 – 36.70
Posterior DMN	13.28 ± 3.49	3.56 – 24.38
ECN	12.35 ± 4.12	4.45 – 35.08
Left FPN	17.84 ± 5.02	7.19 – 35.17
Right FPN	16.81 ± 4.33	6.19 – 35.93

Abbreviations - AD = Axial diffusivity; BMI = Body mass index; CES-D = Centre for Epidemiological Studies Depression Scale; CSF = Cerebrospinal fluid; DMN = Default mode network; FA = Fractional anisotropy; FPN = Fronto-parietal network; GM = Grey matter; HVLT-R = Hopkins Verbal Learning Test Revised; ICV = Intracranial volume; MAP = Mean arterial pressure; MD = Mean diffusivity; MoCA = Montreal Cognitive Assessment; MRI = Magnetic resonance imaging; N = number; PSQI = Pittsburgh Sleep Quality Index; RCF = Rey-Osterrieth Complex Figure; RD = Radial diffusivity; RDI = Recognition discrimination index; TMT = Trail making test; WM = White matter.
Note: Values are Mean ± Standard deviation.
*Raw values are reported, although scores were reverse coded for the analyses.
#measures are intra-network connectivity.

4.3.3 Cognitive and Social Activity Trajectories

Tables 4.2 and 4.3 provide an overview of the fit indices for the latent growth curve models and latent class growth models. Taken together, the quadratic latent growth curve model appeared to provide the most adequate fit for cognitive activity levels (CFI = 0.967, TLI = 0.967, RMSEA = 0.081 (95% C.I. = 0.058 – 0.104)). Similarly, the quadratic latent growth curve model also provided adequate fit for longitudinal measures of social activity levels (CFI = 0.909, TLI = 0.909, RMSEA = 0.145 (95% C.I = 0.123 – 0.167)). The quadratic growth curve models also had better (comparative) fit indices than any of the latent class growth models, for both cognitive activities (AIC = 1229.384, BIC = 1272.91, SSA-BIC = 1241.164) and social activities (AIC = 2371.436, BIC = 2414.962, SSA-BIC = 2383.216). Figures 4.2 and 4.3 demonstrate the pattern of change in activities over the study period.

Table 4.2 Model fit indices for unconditional latent growth curve models.

	AIC	BIC	SSA-BIC	CFI	TLI	RMSEA (C.I.)
Cognitive Activity						
Intercept only	2274.868	2287.925	2278.402	0.096	0.468	0.325 (0.309 - 0.342)
Linear	1620.921	1647.037	1627.989	0.641	0.743	0.226 (0.208 - 0.245)
Quadratic	**1229.384**	**1272.91**	**1241.164**	**0.967**	**0.967**	**0.081 (0.058 - 0.104)**
Social Activity						
Intercept only	2609.447	2622.505	2612.981	0.736	0.845	0.189 (0.173 - 0.206)
Linear	2445.187	2471.303	2452.256	0.853	0.895	0.155 (0.137 - 0.174)
Quadratic	**2371.436**	**2414.962**	**2383.216**	**0.909**	**0.909**	**0.145 (0.123 - 0.167)**

Abbreviations- AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; CFI = Comparative fit index; C.I. = Confidence Intervals; RMSEA = Root Mean Square Error of Approximation; SSA- BIC = Sample size adjusted Bayesian Information Criterion; TLI = Tucker-Lewis Index.

Table 4.3 As the latent growth curve analyses identified the quadratic pattern of cognitive activity as the 'best fitting pattern of growth', we report the results of unconditional quadratic latent class growth models.

	AIC	BIC	SSA-BIC	Entropy	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	LMR-LRT p-value	BLRT p-value
Cognitive Activity												
2 classes	2845.784	2880.605	2855.209	0.86	347	227					< 0.001	< 0.001
3 classes	2575.48	2627.712	2589.617	0.835	85	224	265				0.008	< 0.001
4 classes	2472.393	2542.035	2491.242	0.774	154	53	150	217			0.23	< 0.001
5 classes	2425.45	2512.503	2449.011	0.775	142	39	212	147	34		0.348	< 0.001
6 classes	2399.544	2504.007	2427.817	0.799	203	146	31	44	11	139	0.3531	< 0.001
Social Activity												
2 classes	1688.89	1723.711	1698.315	0.802	339	235					< 0.001	< 0.001
3 classes	1428.067	1480.298	1442.203	0.8	113	317	144				0.0022	< 0.001
4 classes	1349.468	1419.11	1368.317	0.759	78	69	252	175			0.0216	< 0.001
5 classes	1308.241	1395.293	1331.802	0.73	62	73	87	232	120		0.0091	< 0.001
6 classes	*No convergence*											

Abbreviations- AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; BLRT = Bootstrap likelihood ratio test; LMR-LRT = Lo-Mendel-Rubin likelihood ratio test; SSA-BIC = Sample size adjusted Bayesian Information Criterion.

Figure 4.2 Estimated means of cognitive activity levels over time.
The blue band represents 95% confidence intervals.

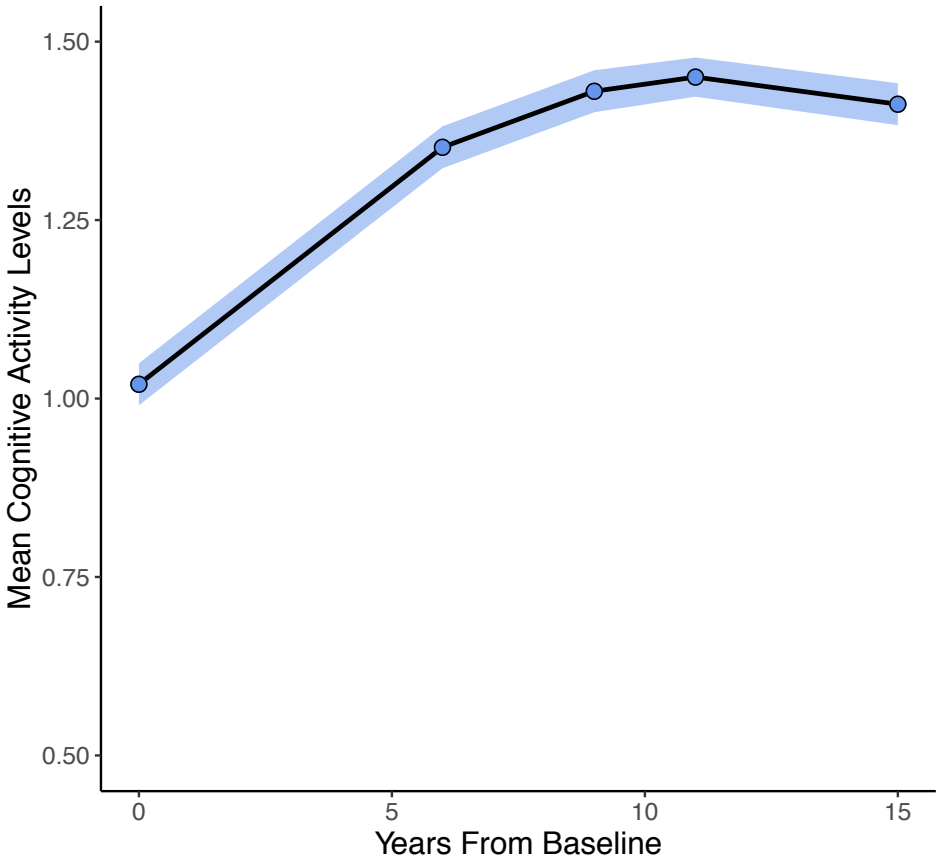
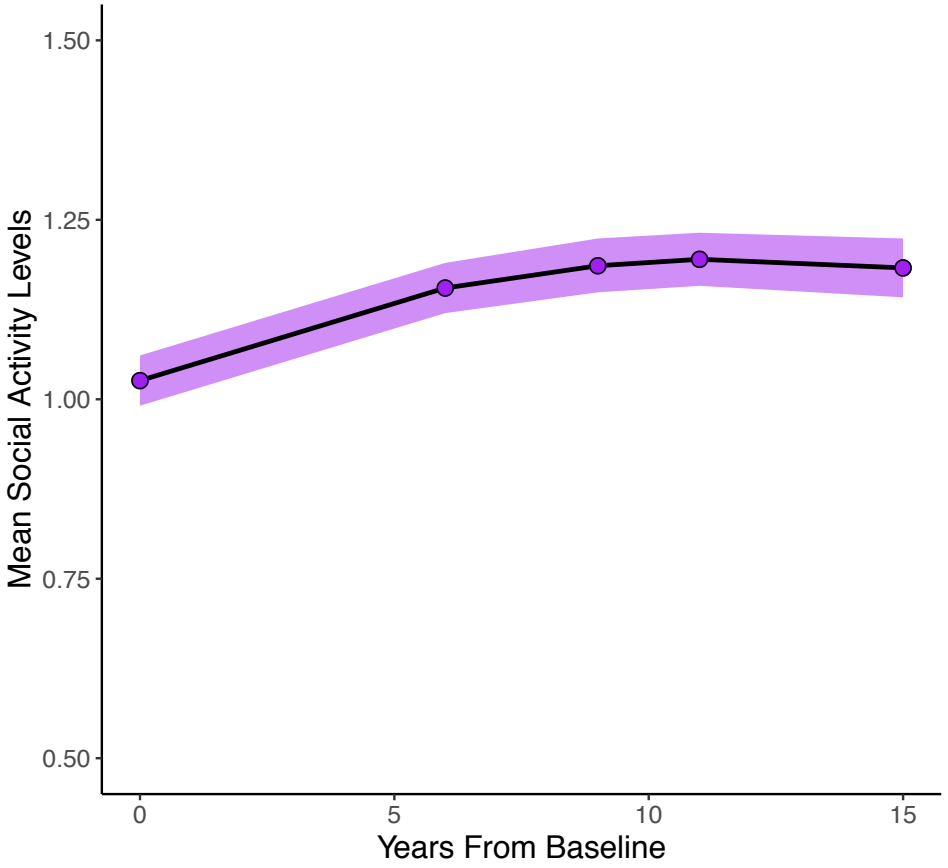


Figure 4.3 Estimated means of social activity levels over time.
The purple band represents 95% confidence intervals.



4.3.4 Activities and Cognitive Function

Adjusting for age, sex, education, marital status and retirement status (i.e. Model 1), a significant positive association was identified between intercepts of cognitive activities and global cognition (B = 0.811, SE = 0.293, β = 0.119, p = 0.006), executive function (B = 1.633, SE = 0.514, β = 0.132, p = 0.002), memory (B = 1.199, SE = 0.567, β = 0.091, p = 0.035) and processing speed (B = 1.413, SE = 0.545, β = 0.110, p = 0.01). The quadratic coefficients for cognitive activities was also negatively associated with global cognition (B = -1.096, SE = 0.509, β = -0.097, p = 0.032), executive function (B = -1.811, SE = 0.894, β = -0.088, p = 0.043) and memory (B = -1.996, SE = 0.982, β = -0.091, p = 0.043). This pattern of results continued to be observed after additional co-variate adjustments (Model 2: p's < 0.05, see table Appendix 4.8). Taken together, this would suggest that higher cognitive engagement was associated with greater cognitive performance in late life, with trajectories following a steeper initial increase in activity followed by a subsequent levelling off or decline in cognitive activity related to better performance on global and domain-specific cognitive function at follow-up.

For social activities, intercepts (Model 1: B = -1.661, SE = 0.523, β = 0.176, p = 0.002) and quadratic coefficients (B = 2.808, SE = 1.030, β = 0.149, p = 0.007) were positively associated with executive function. To interpret the former, higher social activity levels were related to higher levels of executive function in late life. With regard to the latter association, a more pronounced initial increase in social activities followed by a subsequent levelling off or decline in these activities was associated with poorer cognitive function. In other words, a more gradual change in social activities over time (i.e. shallower initial increase and levelling off) was associated with better cognitive performance at follow-up. These associations were also found after adjusting for lifestyle and health co-variates

(Model 2: p's < 0.05, see Appendix 4.9) No other associations for social activities was significant (all p's > 0.05).

4.3.5 Activities and Grey Matter

There was a negative association between quadratic coefficients of cognitive activities and total GM volume (Model 1: B = -0.907, SE = 0.403, β = -0.087, p = 0.025), which also survived further co-variate adjustments (Model 2: p = 0.027; Appendix 4.9). This indicated that trajectories following a steeper initial increase and subsequent levelling off/decline in cognitive activities was associated with higher total GM volume at follow-up.

4.3.6 Activities and White Matter

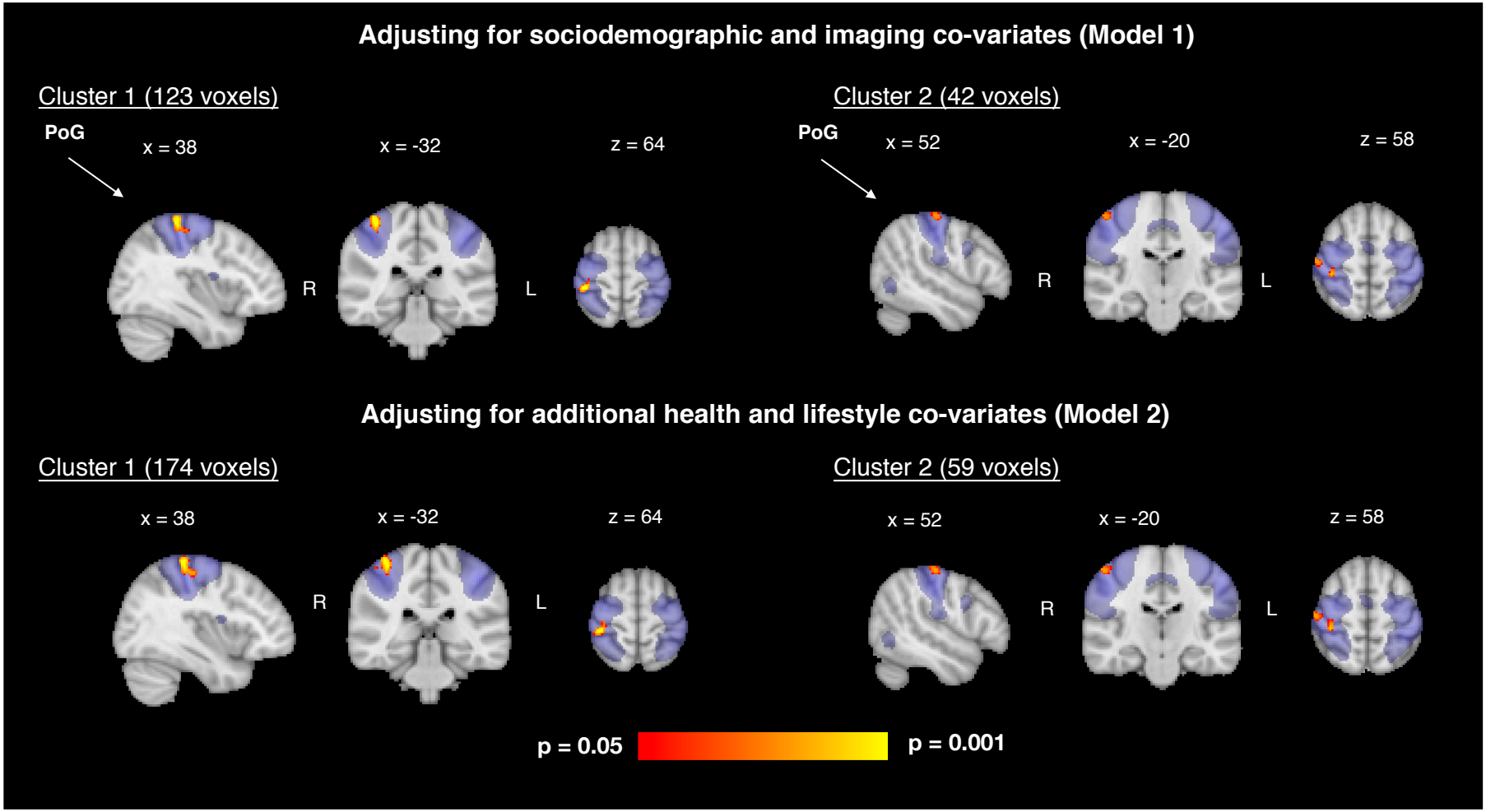
Neither activity type demonstrated any significant associations with the global or voxel-wise indices of FA, AD, MD or RD (p's > 0.05; Appendix 4.8-4.9). In an analysis of 564 participants, the relationship between social or cognitive activities with global WM lesions (WML) was also not significant (p's > 0.05).

4.3.7 Activities and Resting-State Functional Connectivity

No associations were found between activity trajectories and intra-network connectivity or voxel-wise measures of FPN, DMN and ECN functional connectivity (p > 0.05; Appendix 4.8-4.9). None of the post-hoc analyses examining intra-network connectivity outside of the FPN, DMN and ECN were significant either (Appendix 4.10-4.11). However, post-hoc voxel-wise analyses highlighted significant associations involving the sensorimotor network. Specifically, we found a negative relationship between quadratic coefficients of social activities and functional connectivity of the sensorimotor network and two clusters in the right postcentral gyrus (Cluster 1: n. of voxels = 42 p = 0.028, MNI coordinates: x = 52, -20, 58; Cluster 2: n. of voxels = 123, p = 0.014, MNI coordinates: x

= 38, -32, 64; Appendix 4.13; Figure 4.4). The clusters remained significant after further co-variate adjustments (Cluster 1: n. of voxels = 59 p = 0.028; Cluster 2: n. of voxels = 174; Figure 4.4). These associations suggested that social activity trajectories characterized by a steeper initial increase and subsequent levelling off/decline were related to higher functional connectivity between the sensorimotor network and postcentral gyrus, at the MRI follow-up.

Figure 4.4 Results of post-hoc analyses examining additional resting-state networks. Red-yellow clusters overlaid on a MNI152 standard template demonstrate that functional connectivity between the sensorimotor network and the right postcentral gyrus correlated negatively with quadratic coefficients of social activities at a $p < 0.05$ (corrected for multiple comparisons and co-variates). Blue clusters indicate the spatial extent of the sensorimotor network.



Abbreviations- PoG = Postcentral gyrus.

4.4 Discussion

In the present chapter, we aimed to examine whether data-driven approaches could be used to identify sub-groups of individuals following similar patterns of cognitive and social activity levels over mid-life and late life. This chapter also aimed to conduct the first voxel-wise study to examine whether trajectories of cognitive and social activities measured in this period were related to structural and functional MRI measures in old age. Overall, a one-group solution with a quadratic pattern of growth was found to best describe changes in activity levels from mid- to late life, among the Whitehall II imaging sample. We also found associations between the level and change parameters of cognitive and social activities with cognitive function. The curvature of cognitive and social activity trajectories was found to relate with total GM volume and functional connectivity with the sensorimotor network (a post-hoc network), respectively. These results are discussed in more detail for the remainder of this section.

Contrary to our first hypothesis, we did not find evidence suggesting that individuals could be reliably sub-divided into groups based on their longitudinal trajectories, even when controlling for key demographic variables including age, sex and education. Instead, we found that a single-group solution best described the data under examination, suggesting that all Whitehall II participants were relatively homogenous in cognitive and social activity levels over the study period. These results are discrepant with prior studies that also employ mixture modelling, which converge on a five-class linear solution for social engagement (Thomas, 2012, 2011) and leisure activity trajectories (Yu et al., 2018). Key differences in sample characteristics (e.g. age, recruitment source, follow-up length) and study design (e.g. type of model applied) may potentially underlie inconsistencies between the present findings and that of prior studies. For instance, the samples examined by Yu and colleages (2018; mean age = 64 years) and Thomas (2012, 2011; mean age = 70 years) were on

average much older than our sample (i.e. 53 years) at baseline. Further, while Yu and colleages (2018) also applied LCGM to their dataset, these authors combined both cognitive and social activities into a single score and did not appear to test a one-class solution, which may have led to a different conclusion regarding the number of sub-groups identified. For example, while Yu and colleages (2018) also applied LCGM to their dataset, these authors combined both cognitive and social activities into a single score and did not appear to test a one-class solution, which may have led to a different conclusion regarding the number of sub-groups identified. On the other hand, Thomas (2011, 2012) employed growth mixture modelling (GMM) and also compared the fit of models with multiple classes to a single-class model (P.A. Thomas 2018, personal communication, 13th October 2018). GMMs possess certain advantages over LCGM, most notably, their flexibility in modelling *intra-class* variability (Jung and Wickrama, 2008). These models are, however, well known for experiencing convergence problems and producing low entropy values (Jung and Wickrama, 2008), which was observed in a preliminary run of GMMs on our dataset. Higher entropy values and better convergence was observed for our LCGMs, which is why we decided to focus our main analysis on these models in this study. More readily converging models could suggest that the LCGMs simply provided a better fit than the GMMs, although it may also be the case that our data was an 'ill fit' for the GMMs (Berlin et al., 2014). While there are no established guidelines for the minimum sample size appropriate for GMMs, a simulation study (Kim, 2012) found that the percentage of missing data, the number of indicators, the nature of class separation (high versus low), the number of parameters estimated, the number of classes extracted - all influence the required sample size for a GMM study. For instance, in the presence of 20% missing data, 6 classes to extract, 5 indicators, low class separation and 16 parameters to estimate, the required sample size was 3,000 individuals (Kim, 2012). This could be taken to suggest that GMMs perform better with an increasing number of participants. Indeed, the study

conducted by Thomas (2012), used a sample that was more than twice the size of ours (1,667 individuals). If this explanation is true (i.e. that the sample size was insufficient for the GMMs), then we cannot rule out that a single-class latent growth curve model simply provided a better representation of inter-individual variance relative to any of the LCGMs tested, which often extract a higher number of classes (compared to GMMs) to sufficiently model inter-individual variability within a dataset (Twisk and Hoekstra, 2012). To test this interpretation, future studies replicating our results with LCGM and GMMs on larger datasets, are essential.

Competing theories have emerged over the years to explain how leisure activity patterns change as a consequence of ageing. For example, the continuity theory predicts that ageing individuals tend to maintain a similar set of hobbies between mid- to late life, actively adapting to the challenges (e.g. mobility issues) introduced by old age (Atchley, 1989). According to the disengagement hypothesis (Cumming and Henry, 1961), individuals instead become more socially withdrawn as they grow old, driven in part by a shrinking social network. In their literature review, Pinto and Neri (2017) found the greatest support for the disengagement hypothesis, with 21 studies reporting a decrease in social activity levels. Similarly, three of the four studies that Mitchell and colleagues (2012) examined in their coordinated analysis, showed reduced participation in cognitive activities, over time. In this study, we found that Whitehall II members increased their activity levels between mid-life and late life before reaching a period of stability over the observational window. Our results are therefore more in line with the predictions of the continuity, rather than disengagement, hypothesis. These observed increases in activity levels may have been driven by the onset of retirement and uptake of new activities and/or more frequent participation in activities enjoyed earlier in life (Dorfman, 2012). One explanation for our discrepant results with many of the studies reviewed by Pinto and Neri (2017), is that they

have typically applied models *assuming* linear change, and many of these studies were limited to two waves of data. The current chapter demonstrates that future authors should consider applying more flexible models in order to capture non-linear changes in activities. Appropriate datasets need to be selected, however, as at least four time points are required in order to model curvilinear changes using growth modelling techniques (Andruff et al., 2009).

The results involving cognitive outcomes largely seemed to support our hypotheses, in addition to replicating the findings of previous publications (Evans et al., 2018; Kuiper et al., 2016; Yates et al., 2016). Here, we found that higher intercepts of cognitive activities were linked to higher levels of global cognition, executive function, memory and processing speed at follow-up. *Social activity levels*, on the other hand, appeared to have domain-specific associations activities, namely, with executive function. When it came to how *changes in social activities* were related to cognition, the results were more nuanced. Specifically, trajectories consisting of a steeper initial increase followed by a levelling off/decline in social activities were found to associate with *poorer* performance on tests of executive function. Conversely, *cognitive activity trajectories* following this pattern were instead related to *better* performance on measures of global cognition, executive function and memory. Although speculative, these results could be taken to suggest that while *maintaining* high levels of social activities may be important for executive function, the positive 'effects' conferred through initially increasing cognitive activities may outweigh the negative 'effects' of withdrawing from these at a later date. Given that we are the first to demonstrate this association, it is important that future studies examine how non-linear changes in different activities relate to cognitive function over time. If our results are replicated, it may be sensible to recommend that any lifestyle-based intervention developed to promote healthy ageing should be designed to be adhered to by wide range of age groups

and to be age adaptable. For example, community-based programmes aimed at preventing social isolation among older adults, could provide provisions (e.g. free transportation or meals) to ensure that they are as accessible as possible and to encourage long-term attendance among this cohort.

We found that a steeper initial increase and subsequent levelling off/decline in cognitive activities were related to higher total GM volume, although no parallel associations with voxel-wise GM were identified. This discrepancy may be attributed to small effects that are undetected after multiple comparison corrections in the latter voxel-wise analyses. Although these results should be interpreted with caution, they might reflect that the positive 'effects' gained through increasing activity levels between mid-life and late life are sustained even after an individual withdraws from these activities at a later date. Post-hoc analyses further revealed that social activity trajectories following a more curved pattern over time were associated with higher functional connectivity between the sensorimotor network and right postcentral gyrus (which forms part of this network), at the MRI follow-up. No associations were identified with average intra-network connectivity of the sensorimotor network more generally, suggesting that this observation was specific to connectivity of the postcentral gyrus. We are cautious in interpreting these results due to their post-hoc nature, although highlight this network as one that may be of interest to future studies. While it remains unclear as to what may be driving these associations, we propose that the light physical activity (e.g. walking) done when undertaking certain social activities (e.g. visiting friends/family or going to a community centre), could be an explanatory factor. Although we had adjusted for the time spent in moderate-to-high intensity physical activities, participation in less physically demanding activities was not taken into account in the present analysis.

Otherwise, contrary to our hypothesis, we did not find any associations between the level or change in cognitive and social activity levels and any neuroimaging marker of brain structure or functional connectivity. While resting-state literature is scarce, prior studies using structural MRI have also identified null associations between mid-life or life-time activities and late life GM volume (Foubert-Samier et al., 2012; Vemuri et al., 2016), WM integrity (Foubert-Samier et al., 2012; Vemuri et al., 2016), and WM lesions (Valenzuela et al., 2008; Wirth et al., 2014) and may suggest alternative neural mechanisms at play, such as the build-up of β-amyloid plaques and hypometabolism (Arenaza-Urquijo et al., 2015; Landau et al., 2012; Wirth et al., 2014). Several studies are in disagreement with our MRI results, though, instead suggesting that the link between activities and the brain are widespread, spanning across multiple modalities. Indeed, Chapter 2 pooled together much of this work, identifying consistent links between socio-intellectual activities, WM (volume and lesions) and hippocampal volume. While the meta-analyses were based on a single global volumetric measure provided by each study (e.g. total GM volume) the corresponding systematic reviews highlighted observations from several studies suggesting voxel-wise associations between activities, GM and WM microstructure (Bartrés-Faz et al., 2009; Köhncke et al., 2016; Suo et al., 2012; Valenzuela et al., 2008). One explanation for our results is that the imaging outcomes were measured cross-sectionally, even though longitudinal changes in brain structure and functional connectivity are potentially more sensitive correlates of social and cognitive engagement. This is supported by the results of Köhncke and colleagues (2016), who did not find any level-level associations between social activities and WM microstructure, although found that *changes* in social activities were related to *changes* in FA and MD, within the corticospinal tract. Future longitudinal MRI studies are therefore required to evaluate whether our results are replicable. Another explanation for our non-significant findings is the assessment and operationalization of activities used within this study. For example, while our questionnaire probed commonly

assessed activities, the measure itself was specific to the Whitehall cohort. An essential next step will be to examine *longitudinal trajectories* of activity levels with psychometrically validated questionnaires (e.g. Cognitive Activities Scale (Wilson et al., 1999)) or even using objective assessments such as wearable devices (Anatürk et al., 2018).

4.5 Strengths and Limitations

The main strengths of this study are that it examines data collected from a well characterised and large sample of adults, uses multi-modal imaging, and examines five measurements of activities, spanning an average of 15 years. These aspects of the study enabled us to conduct a detailed examination of the relationship between leisure activities and brain structure, functional connectivity and cognition, in a greater level of detail than previous publications.

This study does, however, have several weaknesses. For instance, activity levels were measured using a self-report questionnaire, the consequences of which have been previously discussed. Noise introduced by our measurement tool may also explain the discrepant fit indices for the quadratic growth curve model when applied to the social activity data. While the comparative fit measures (e.g. BIC, CFI and TLI) indicated adequate fit, the RMSEA contradicted these indices (i.e. > 0.1). The RMSEA, however, has previously been shown to perform poorly when the degrees of freedom of a model are small (i.e. = 1; Kenny et al., 2015). Yet, this is not likely to explain the results of the present study as our quadratic growth models each had 10 degrees of freedom. Nevertheless, as the majority of fit indices appeared to suggest better comparative fit and adequate global fit of the curvilinear growth curve model, we defend our decision to select it as the 'best fitting' model in the present study. Readers are, however, reminded to interpret our results (for social activities) with caution. Other issues that may be raised with the analyses

performed here is that (a) years from the baseline assessment were used as the time scale, rather than age, and (b) participants were treated as if they were assessed at *exactly the same time for each assessment*. With regard to (b) first, our data violate these model assumptions as, in reality, there was variation between each individual's assessment dates. To accommodate these inter-person differences, preliminary analyses were run, in which LGCMs and LCGMs with individually varying time points were considered (results not shown). However, these models could only provide *relative fit indices* (e.g. BIC; i.e. allowing models to be compared to one another) with no indication of *global fit indices* (i.e. how well a given model fits the data). This is also an issue reported in previous publications (e.g. Berlin et al., 2014). Considering that a given model can have excellent *comparative* fit but very poor *global fit*, the main analyses instead employed growth models that treat data as *time-structured* (i.e. everyone assessed at the same time; van de Schoot et al., 2017), so that these latter group of fit indices could factor into model selection. Relatedly and with regard to (a), as there was up to a twenty-year difference in the age of participants at each assessment point, this variable was not used to denote the time scale in our analyses. Instead, the average years from baseline was selected, due to there being far less variation in the assessment dates between individuals. While there has been a recent push towards adopting growth models that take into account *time-unstructured data* (i.e. everyone assessed at different times; van de Schoot et al., 2017), fewer available indices to inform model selection may deter researchers from using these methods. We instead recommend that future researchers employ multi-level, rather that SEM-based, models to address data in which there is substantial inter-individual differences in assessment dates, as these appear to perform better under certain conditions and provide several global indices to evaluate goodness of fit (e.g. RMSEA; Liu et al., 2015).

Another disadvantage that requires acknowledgement is the use of composite measures for activities, which may have attenuated the independent effects of individual activities. A 'healthy volunteer' effect (Delgado-Rodriguez, 2004) parallel to Chapter 3 was also found, with participants included in the analyses significantly younger, more educated, more likely to be married and had a higher MoCA score, compared to excluded individuals. Due to there being an overrepresentation of males in our sample, it is also likely that the present results are restricted in their generalizability to the wider older adult population. Finally, no causality can be inferred based on the activity-cognition findings reported, due to the correlational nature of the data. Reverse causation may therefore provide an alternative account for our results. For instance, individuals in the early stages of cognitive impairment may start to withdraw from their social commitments as these activities become too strenuous and demanding to maintain regularly.

4.6 Conclusion

Consistent with our cross-sectional analyses in Chapter 3, we report associations between cognitive activity trajectories and global cognition, executive function and memory, finding that this type of activity was only linked to total GM volume. We also report domain-specific associations between level and change parameters of social activities, with executive function. At a voxel-wise level, no associations were found between activity trajectories and brain structure or functional connectivity of the DMN, ECN or FPN. Post-hoc analyses, however, indicated that social engagement trajectories were related to higher connectivity between the sensorimotor network and postcentral gyrus. Overall, our findings suggest that *maintaining* high social and cognitive levels may be crucial for healthy cognitive ageing. Furthermore, *increasing* cognitive and social activities could further be related to additional gains in cognition although suddenly withdrawing from one's social life is likely to impede cognition in the later years of life. This chapter also demonstrates

how longitudinal modelling can be applied to better understand the link between activities and the ageing brain and provides important considerations for lifestyle-based interventions designed to support old age cognition.

CHAPTER 5

Associations Between Individual Activities During Mid-life and Late life and MRI Measures of the Ageing Brain in the UK Biobank Cohort

Contents

Abstract 152

5.1 Introduction 154

5.2 Methods 156

5.3 Results 169

5.4 Discussion 178

5.5 Conclusion 186

Abstract

While composite measures of leisure activity levels provide meaningful insights into the *combined* 'effects' of different activities on the ageing brain, intervention development may be better informed by approaches that consider their separate contributions. Accordingly, this chapter aims to evaluate whether mid-life and late life participation in common activities, are linked to measures of brain structure, functional connectivity and cognition in early old age. To address this aim, we examined data collected from 7,158 participants of the UK Biobank study.[3] Weekly participation in six leisure-time activities was assessed, which included: visiting friends or family; going to the pub or social clubs; attending gyms or sports clubs; taking part in religious activities; attending educational classes; leisure-time computer use. Along with completing a set of questions on their activity habits at two time

[3] The UK Biobank team was responsible for participant recruitment and data collection for this study. I planned, conducted and interpreted the analyses described in this chapter.

points, participants had a 3T MRI brain scan and completed a cognitive battery, at the follow-up phase (mean follow-up duration = 8 years). Weekly computer use at mid-life correlated with larger volumes of the left putamen and performance on the fluid intelligence, alphanumeric and numeric trail making tasks and prospective memory score. Frequent attendance at a sports club or gym at mid-life was associated with stronger connectivity of the sensorimotor with the lateral visual and cerebellar network. Weekly attendance in educational classes was also linked with fluid intelligence. Overall, our study highlights several activities that may have a role to play in maintaining brain structure, functional connectivity and cognition, in late life. These results suggest that future RCTs should consider integrating socially and intellectually stimulating activities when designing multi-modal interventions to promote brain health in older adults a decade later.

Keywords: Leisure activities, Brain, MRI, Ageing, Cognition, UK Biobank

5.1 Introduction

To date, the most common method used to characterize leisure activity levels has been to create a composite score across responses on a variety of activities. This method has been important for shedding light on the potential *additive effects* of activities that share common features with one another, such as a social demanding nature. However, it may be short-sighted to treat all activities as though they contribute equally - or even in the same direction - towards brain or cognitive reserve. While we have attempted to account for such known differences between various activities by weighting duration/frequency responses by their respective social/cognitive demand in Chapters 3 - 4, the composite nature of the leisure activity scores used still prevents sensitivity to any activity-specific effects. If one activity were to have positive associations with a set of MRI markers, whilst another had inverse associations with these same outcomes, the composite score produced from these activities may well produce no association at all to the outcomes of interest. This account could explain the results of Schultz and colleagues (2015), who found that that while a summary measure of cognitive activities was unrelated to regional GM volume, frequently participating in games (e.g. cards, checkers, crosswords) was associated with greater regional GM volume, which included the caudal and rostral anterior cingulate, caudal middle frontal and posterior cingulate cortices. Another important advantage of adopting a fine-grained approach within an observational setting is that it may begin to pinpoint particular activities that are strong predictors of brain health (and those that are redundant), to ensure that any multimodal interventions subsequently assessed by RCT design, integrate the identified activities into the intervention. A study led by Fancourt and colleagues (2018) provides a good example of the applications of this approach in practice. These researchers examined data collected from 3911 individuals from the English Longitudinal Study of Ageing and found that adults who visited museums, art galleries and exhibitions on a regular basis, had a lower incidence rate of dementia over the course of

10 years (Fancourt et al., 2018). The association between cultural activities and dementia incidence also appeared to be robust, as it was detected even after adjusting for how frequently these individuals were involved in community-based activities (e.g. social clubs, volunteering, sports clubs), alongside sociodemographic and health-related co-variates. In another study of 446 individuals, those who reported longer hours of television viewing in mid-life were appeared to have a higher risk of developing Alzheimer's disease (Lindstrom et al., 2005).

Importantly, a study that aims to evaluate whether different activities independently relate to markers of brain health will require a much larger number of univariate tests, compared to an approach that focuses on a single leisure activity score. With an imaging sample that currently exceeds several thousand individuals, the UK Biobank study offers the statistical power to examine these associations of interest. This study also possesses a further advantage: it provides measures of activities that are traditionally used to create social activity scores (e.g. visiting friends and family, attending a group activity) and to a lesser extent, cognitive activity scores (e.g. leisure-time computer use, attending educational classes). As a result, the type of analysis proposed here may be useful for informing on whether these activities should be combined, as is often done in neuroimaging and epidemiological studies, or whether a more refined focus should be taken, examining the independent effects of different activities on the brain.

5.1.1 Aims

The aim of this chapter is to examine whether common activities, measured at both mid-life and late life, independently related to MRI measures of GM volume, WM microstructure, WM lesions, resting-state functional connectivity and cognitive function in late life. Based on the results of Chapters 3 – 4 and prior review findings (Evans et al.,

2018; Wang et al., 2012; Yates et al., 2016), we predict that more frequent participation in each of the activities assessed will correlate with better performance on tests of cognitive function. Prior work also informs the hypothesis that mid-life activities may have more consistent associations with cognition, relative to late life (Chan et al., 2018; Gow et al., 2017). As there is an absence of evidence, it is not possible to make activity-specific predictions, although we would expect to find an activity high in both social and cognitive demand to possess the strongest associations with the outcomes of interest (e.g. visiting friends and family; based on Chapter 2 results).

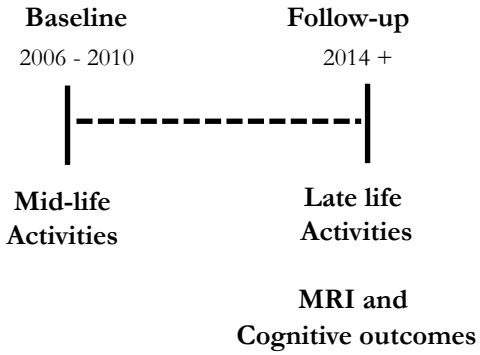
5.2 Methods

5.2.1 Sample Characteristics

Data were provided by participants enrolled in the UK Biobank study, a large-scale prospective cohort study. This study recruited over 500,000 individuals between the ages of 40 – 69 years old and invited them to one of 22 assessment centres across the United Kingdom (2006 – 2010; Sudlow et al., 2015). Participants were asked to complete a range of assessments including detailed lifestyle questionnaires, cognitive tests, physical measures (e.g. BP and mobility tests), provided biological samples (e.g. blood, urine, saliva) and also agreed to allow access to their National Health Services (NHS) health records. Since 2014, a sub-sample of participants have been invited back to undergo a single session of MRI scanning of the brain, body and heart, with the goal of reaching 100,000 scanned individuals by 2020. The overarching aim of this imaging extension is to identify candidate biomarkers of age-associated diseases, such as Alzheimer's Disease (Miller et al., 2016). This sub-study is an ongoing effort, with regular data releases made available to researchers. At the time of chapter preparation, imaging data from a total 15,000 participants had been released (January 2018).

In the present analyses, we examine data collected from two phases: at recruitment (2006 – 2010) and MRI assessment (2014+; Figure 5.1). Participants were scanned at the assessment sites located at either Stockport (Manchester) or Newcastle. The UK Biobank study received ethical approval from the NHS National Research Ethics Service (Ref 11/NW/0382) and all enrolled participants gave their informed and written consent.

Figure 5.1. A timeline of the study assessments and variables of interest examined in the current analyses.



Abbreviations- MRI = Magnetic resonance imaging.

5.2.2 Inclusion and Exclusion Criteria

The main sample consisted of individuals who had completed an MRI assessment, had provided information on all of the leisure activities and sociodemographic, health and lifestyle variables of interest and did not have an ICD-10 diagnosis of stroke or dementia (for flowchart, see Appendix 5.1). Individuals with incomplete data on activity levels at baseline or follow-up (n = 6,771), lifestyle and health (n = 7,169), structural MRI (n = 11,392) or functional MRI (n = 1,988) or who had a diagnosis of stroke or dementia (n = 17), were not included. Only a quarter of the main sample (24.23%) had completed the cognitive battery and were therefore analysed separately as a sub-sample.

5.2.3 Activities

Activity levels were assessed through items delivered on a touch screen tablet. Respondents were required to indicate from a list of activities, those that were undertaken on a weekly (or more frequent) basis. The activities measured consisted of going to a pub or social club, participating in a religious activity, attending adult education classes and going to a sports club or visiting the gym. A fifth item, which asked individuals to indicate whether they regularly participated in "other group activities" was excluded due to the ambiguity of the question posed. Responses on these four items were coded as a "1" for weekly participation, or a "0" for irregular/ no participation.

Separately, respondents were also asked to indicate how frequently they received or made friend or family visits, with possible answers consisting of: "almost daily", "2-4 times a week", "about once a week", "about once a month", "once every few months" or "never or almost never". Leisure-time computer use was included as another item, with participants asked to indicate the number of hours (per week) they committed to this activity in a typical day. To avoid biases introduced by differences in the granularity of our various activity scales, we binarized responses on these items. Specifically, we assigned a code of "1" for individuals who received or made friend and family visits at least once a week, and an assignment of "0" for those who visited friends and family less frequently than once a week. Weekly or more frequent family/friends were coded as "1". Similarly, participants reporting 0 hours of daily computer use were coded as "0", whereas, those reporting any amount of daily use where grouped as weekly engagers (i.e. "1"). For all activities, answers corresponding to "do not know" or "prefer not to answer" were coded as missing data.

5.2.4 Cognitive Function

A 15-minute battery of cognitive assessments specifically designed for the UK Biobank study was delivered to participants via a touch screen tablet (Cornelis et al., 2019). Although the self-administered and unsupervised nature of these tests may call into question the reliability and validity of these tests, a recent study of 160 adults (Fawns-Ritchie and Deary, 2019) shows that the UK Biobank cognitive assessments have moderate-to-high test-retest reliability and moderate-to-high concurrent validity, as indicated by correlations between each of these measures with that of validated and standardized tests, delivered in a face-to-face setting. The selection of cognitive tests examined in the present study was guided by both the Whitehall battery examined in Chapters 3 – 4, in addition to prior research (e.g. Chan et al., 2018; Cornelis et al., 2019). Some tests, for instance of language fluency, were only administered at the pilot phase of the UK Biobank, and so were excluded here. Overall, several previous studies have demonstrated that the cognitive tests examined here are sensitive to age-related differences in performance (Cornelis et al., 2019; Fawns-Ritchie and Deary, 2019).

The cognitive battery included a 13-item questionnaire designed to assess *Fluid Intelligence*. This questionnaire included reasoning/logic items that each had 5 multiple choice options. Participants were required to select one of these responses within a 2-minute period. For example, one of the items asked: "Relaxed means the opposite of?", with the response options consisting of "calm", "anxious", "cool", "worried" and "tense". The outcome of this test was the total number of questions answered correctly.

Numeric and alphanumeric trail making tasks were also completed by a portion of the total sample. This task presented participants with 25 circles distributed across the screen, which contained either numbers ranging from 1-25 (numeric trail) or a mix of numbers and letters

(alphanumeric trail). Participants were asked to connect the circles from the smallest to largest numbers in one task (numeric trail) or to alternate between numbers and letters in an ascending sequence in the other (alphanumeric trail). The outcomes on these tasks were the time taken to complete the trail, with lower values reflecting a faster completion time. Individuals who spent ≥ 250 seconds on these respective tests, were excluded (Hagenaars et al., 2018).

A *digit span* test was also administered. Individuals were presented with a sequence of digits, which they were instructed to recall in a reverse order (starting with the last digit first) after a short delay. Each time the sequence of digits was recalled correctly, the number of digits to be remembered increased by 1. The number began at 2 digits and increased to a maximum number of 12 digits. The test terminated as soon as errors on a given trial was made. The outcome here was the maximum number of digits recalled.

Another test, known as *pairs matching*, relied on the use of computerized cards. Here, participants were presented with a set of cards (organized into 3 rows, 4 columns) and were briefly shown the symbols that the cards contained before they were turned face down. Each card had a matching pair, with the task requiring respondents to match the six pairs of cards from memory while making as few errors as possible. The main outcome was the number of incorrect matches made.

The *prospective memory* test began with a screen containing four colored symbols: a blue square, a pink star, a grey cross, and an orange circle. Text also accompanied the four symbols that informed participants that they would see the screen again at the end of the cognitive battery, and they would be asked to press the blue square. The text instructed participants that rather than touching the blue square (as the later instructions dictated),

they should instead press the orange circle. The outcome was whether or not participants had responded corrected (i.e. touched the orange circle) on the first attempt.

A *symbol digit matching* task was also administered. In this task, individuals were presented with a set of grids with each box containing a symbol. Participants were required to match each symbol with a unique digit, with the correct symbol-digit matches detailed in a key that was available throughout the 1-minute response period. The outcome was the number of correct symbol-digit matches made (excluding the first 8 items that served as training material).

Finally, a *simple reaction time* task was also completed, which is analogous to the card game 'Snap'. For this assessment, participants were presented with a pair of cards (total number of pairs = 12) and were required to press a button as quickly as possible whenever the symbols on the cards were matching. Four training trials were first completed, after which 7 recorded trials were administered (4 of which contained matching pairs). The key outcome was the mean response time (in seconds) across the 4 trials containing matching pairs.

5.2.5 Demographics and Health Variables

All demographic (including age and sex), lifestyle and health variables were collected at baseline, unless otherwise stated. Educational level was assessed by asking respondents whether they possessed one or more of the following qualifications: "college or university degree" (= "5"), "NVQ or HND or HNC or equivalent" (= "4"), "other professional qualifications (e.g. nursing, teaching)" (= "4"), "A levels/AS levels or equivalent" (= "3"), "O levels/ GCSEs or equivalent" (= "2") and "CSE or equivalent" (= "1"). From this information, we created a variable indicating the highest qualification earned. Occupational

status was coded according to the Standard Occupational Classification, where participants were divided into one of nine occupational groups: "Manager and Senior Officials" (= "9"), "Professional Occupations" (= "8"), "Associate Professional and Technical Occupations" (= "7"), "Administrative and Secretarial Occupations" (= "6"), "Skilled Trades Occupations" (= "5"), "Personal Service Occupations" (= "4"), "Sales and Customer Service Occupations" (= "3"),, "Process, plant and machine operatives" (= "2") and "Elementary Occupations" (= "1"). An additional category, reflecting the lowest level of this variable included those who were retired, unemployed, looking after home and/ or family, unable to work because of sickness or disability, full or part time student (= "0").

Frequency of alcohol intake (over the last year) was measured as "daily or almost daily" (= "5"), "three or four times a week", "once or twice a week", "one to three times a month", "special occasions only" or "never" (= "0"). Sleep duration was measured as the hours of sleep within an average 24-hour period. Body mass index (BMI) was calculated as: (weight [kilograms]/height [metres])^2. Mean Arterial Pressure (MAP) was also calculated based on the systolic and diastolic indices measured with an electronic tool (systolic blood pressure + 2* diastolic blood pressure/3). Note that in the case where two measurements of diastolic/systolic measures were available, an average over these measures were created before calculating the MAP. If only a single assessment was available, then this was used for to calculate the MAP. Diagnoses of depressive (e.g. major depression) and anxiety disorders (e.g. social anxiety), coded according to the World Health Organization's International Classification of Diseases manual (ICD-10), over the study period were also taken into account. Until April 2010, ICD-10 was used, with ICD-10 4th edition used from April 2010 to date (Wu et al., 2019). An index of social isolation was further included (Shankar et al., 2013b), assessed as the total number of individuals living in the household (alongside the participant).

5.2.6 MRI Data Acquisition and Pre-processing

5.2.6.1 MRI Data Acquisition

Participants were scanned on a Siemens Skyra 3T (software VB13) with a Siemens 32-channel head coil at one of two identical study sites (i.e. Stockport and Newcastle) operating 7 days a week (with 18 participants scanned per day). T_1-weighted images, diffusion-weighted images, T2 FLAIR images and resting-state functional images were examined.

T1 images were acquired with a resolution of 1 x 1 x 1 mm and a field of view of 256 mm, in the sagittal plane with a 3D magnetization-prepared rapid gradient echo (MPRAGE). The inversion and repetition times were 880 ms and 2000 ms, respectively. Diffusion-weighted images were collected using a spin-echo echo planar imaging sequence, with 2 mm isotropic voxels, a 104 x 104 mm field of view, an echo time of 92 ms, repetition time of 3600 ms and a multiband acceleration factor of 3 (i.e. three slices acquired at a time Miller et al., 2016). Five b0 images were collected, in addition to images acquired with two separate b-values (50x b = 1000 s/mm^2 and 50x b = 2,0000 s/mm^2), which amounted to 100 diffusion-encoding directions. T2-weighted FLAIR imaging was additionally acquired with 3D SPACE in the sagittal plane (resolution = 1.05 x 1 x 1 mm, field of view = 192 x 256 x 256 mm; inversion time = 1800 ms, repetition time = 5000 ms). Finally, resting-state fMRI images were acquired with a gradient echo-echo planar imaging (GE-EPI) using a multi-slice acceleration of 8 and a flip angle of 52° (2.4 x 2.4 x 2.4 mm voxels; field of view = 88 x 88 x 64 mm, 490 timepoints, repetition time = 0.745 seconds, echo time = 39 ms).

5.2.6.2 MRI Data Pre-processing

Measures of brain structure and functional connectivity, or Image Derived Phenotypes (IDPs), were generated using FMRIB's Biobank Pipeline (version 1.0, Alfaro-Almagro et

al., 2018). For a detailed description of the imaging protocol and pre-processing steps, please see Alfaro-Almagro et al. (2018) and Smith et al. ((2018), http://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf).

The T1-weighted images were first defaced to anonymize the images. The size of field of view was then reduced to remove voxels containing non-brain tissue, using a combination of FSL's Brain Extraction Tool (Smith, 2002); linear registration (Jenkinson et al., 2002; Jenkinson and Smith, 2001), and the MNI152 "nonlinear 6th generation" standard space T1 template (http://www.bic.mni.mcgill.ca/ServicesAtlases/ICBM152NLin6). Gradient distortion correction was also applied at this point. Next, nonlinear registration was performed with FNIRT (Andersson et al., 2007) to calculate the T1-to-MNI152 warp transform, with a custom brain mask as a reference image. Using the inverse of the warp transform, the standard space brain mask was then transformed into each individual's native T1 space in order to brain extract for each individual. FAST (Zhang et al., 2001) was subsequently applied to fulfil two objectives on the brain extracted T1 images: (1) segment the images based on tissue types (i.e. GM, WM and CSF) and (2) generate a bias-field corrected image. Partial volume estimates of GM from FAST were parcellated into 139 GM ROIs, using a combination of the Harvard-Oxford cortical and subcortical atlases (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and Diedrichsen cerebellar atlas (http://www.diedrichsenlab.org/imaging/propatlas.htm) to facilitate parcellation. FSL's FIRST was also employed to extract volumetric estimates of key subcortical structures, including the hippocampus, amygdala, thalamus, pallidum, caudate, putamen (Patenaude et al., 2011). Note that the corresponding FAST-extracted ROIs for these subcortical regions were excluded. For a list of all of the regional GM IDPs examined in this study, see Appendix 5.2. Finally, in order to derive an estimate of head size (used as a co-variate in the present analyses), the pre-processed T1 images were separately submitted to a

SIENAX (Structural Image Evaluation, using Normalisation, of Atrophy: Cross-sectional; (Smith et al., 2002).

For the raw diffusion-weighted images, EPI distortions and eddy currents/outlier slices were addressed with FSl's topup (Andersson et al., 2003) and eddy, respectively (Andersson and Sotiropoulos, 2016, 2015). The next step was to apply gradient distortion correction (developed by HCP and FSL) to remove artefacts introduced by head motion. DTI fit (Basser et al. 1994) was applied to derive FA and MD images for each participant. The pre-processed diffusion-weighted images were subsequently submitted to a tractography-based analysis. Specifically, BEDPOSTX (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide) was used, which is a method for intra-voxel modelling of multi-fibre tract orientations with the capacity to estimate up to three fibre orientations within a voxel. The output of BEDPOSTX were then fed to PROBTRACKX (Behrens et al., 2007, 2003; Hernández et al., 2013; Jbabdi et al., 2012), a tool that conducts probabilistic tractography (implemented with a crossing-fibre model), which is currently able to map 27 major tracts using start/stop ROI masks defined by AutoPX (de Groot et al., 2013). The tracts included the cingulum bundle, thalamic radiations, longitudinal fasciculi with a full list available in the Appendix 5.3. As the results of both of these tools are in native space, non-linear transformations were applied to bring the results into 1mm standard MNI space. The IDPs made available after these pre-processing steps were the weighted-mean FA and MD for each of the 27 tracts. After defacing, the T2 FLAIR structural images were registered to the T1-weighted images using FLIRT (Greve and Fischl, 2009). The transforms generated were then used to register the FLAIR images to MNI space. An estimate of total WM hyperintensity volume was

generated by feeding the T2-weighted FLAIR and T1-weighted images to the BIANCA tool developed by Griffanti et al. (2016).

The pre-processing steps involved motion correction (via MCFLIRT, Jenkinson et al., 2002), grand-mean intensity normalisation of the 3D dataset, high pass temporal filtering, EPI and GDC unwarping. ICA+FIX processing were applied to remove the presence of individual-level structured artefacts (Beckmann and Smith, 2004; Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). The images were then brought into T1 space and then standard MNI space, using FLIRT (with a BBR cost function (Greve and Fischl, 2009). Next, low-dimensionality Group ICA (n. of components = 25) was applied to the pre-processed functional images of 4,162 individuals (Alfaro-Almagro et al., 2018) in order to derive group-level spatial maps of large-scale resting state networks. Twenty-one of these components were deemed to be 'signal' of interest (see Appendix 5.4 for an overview of components; hand labelled by Melis Anatürk (M.A.) and checked by Claire Sexton (CES) and Sana Suri (SS) and submitted to a FSLNETS analysis. This tool was used to generate a 21x21 matrix (i.e. connectomes) representing the correlations (i.e. edge or connectivity) between pairs of large-scale functional networks (i.e. nodes). Partial correlations were used as they provide a more direct estimate of the connectivity between two nodes, with estimates adjusted for the connectivity of all other nodes in the connectome. Estimates of partial correlations were derived with an L2 Regularization (rho = 0.05 in the Ridge Regression option in FSL Nets). All values were transformed from Pearson's correlations to z-statistics. Prior to the analysis, we used a method validated by prior studies (Shen et al., 2018; Smith et al., 2015) to improve the interpretability of our results. Specifically, values for individuals were multiplied by the sign of their mean edge value, in order to give an index of *absolute connectivity,* with higher values reflecting stronger connections. Head

motion (derived from McFLIRT) represented the mean relative displacement measured during the acquisition of functional images and was used here as a co-variate.

5.2.7 Statistical Analysis

5.2.7.1 Comparisons of Included and Excluded Participants

Independent t-tests (or Welch's test in the presence of unequal variances) or chi-squared tests were applied to compare included and excluded participants on sociodemographic, lifestyle and health variables. Test selection was determined by whether the variables were continuous or categorical.

5.2.7.2 Main Analysis

All analyses were done in R (version 3.5.2). The lm function in R (https://www.rdocumentation.org/packages/stats/versions/3.6.0/topics/lm) was used to fit a series of linear models to address the main research question. Specifically, each activity (i.e. going to a pub or social club, participating in a religious activity, attending adult education classes, attending sports club/gym, visiting friends/family and leisure-time computer use) was evaluated as separate predictor of the imaging and cognitive outcomes of interest, after co-variate adjustments, which were entered in a step-wise manner. Model 1 consisted of one of the six activities, co-varied for the effects of age, sex, education, occupational status, scanner site, mean head motion and head size. For the analysis of cognitive function, head motion and head size were not included as co-variates. Model 2 included all of the variables in Model 1, in addition to further co-variate adjustments, including BMI, BP (MAP), frequency of alcohol intake, sleep duration, the presence of depressive or anxiety disorders and the number of individuals living in a household. Model 3 then integrated all of the variables from Models 1 and 2 and also took into account mutual adjustments between each of the activities of interest. The imaging dependent

variables that were examined consisted of total and regional GM volume (142 IDPs), total WM volume and lesions within this tissue (2 IDP), WM integrity (FA and MD, 54 IDPs), and functional connectivity between large-scale resting-state networks (210 IDPs). A total of 8 cognitive outcomes were also assessed. Prospective memory was the only exception where an alternative to the linear regression was performed, due to the binary nature of this variable (correct/incorrect answer). Binomial logistic regression was instead conducted, where the outcome of interest was the log odds of completing the prospective memory task correctly, at first attempt.

The distributions of all variables were checked for normality and correlations between predictors was also examined, to diagnose cases of multicollinearity. Due to a presence of non-normality, several variables were log-transformed before being entered into the analysis (e.g. total WM lesions; numeric and alphanumeric trail making task performance, total errors on the pairs matching tasks). As a large number of univariate tests were conducted, we report and discuss only the results that survived FDR-corrections, with a full table of associations that were significant at a $p_{uncorrected} < 0.05$ level in Appendices 5.6-5.13. FDR corrections were applied across imaging modalities, for activities measured at the same time-point (mid-life; late life). FDR corrections were applied separately for the analysis of cognitive tests, as this was conducted in a smaller sample to the main analytical group. To facilitate these corrections, the p.adjust function in R was applied (https://www.rdocumentation.org/packages/podkat/versions/1.4.2/topics/p.adjust-methods), with FDR q values < 0.05 considered significant (Cox et al., 2019). We report unstandardized beta-coefficients (B), their standard error (SE), standardized beta coefficients (β), unadjusted p-values ($p_{uncorrected}$) and FDR q-values. Standardized beta coefficients were derived using the package lm.beta (https://cran.r-project.org/web/packages/lm.beta/lm.beta.pdf). For the logistic regression results, the

odds ratio and 95% confidence intervals (95% C.I.) are reported.

5.3 Results

5.3.1 Sample Characteristics

A total of 7,152 participants were included in the analysis of neuroimaging outcomes. Participants were on average 56.39 years old (SD = 7.31) at baseline (i.e. "mid-life"), and an average age of 63.94 years old (SD = 7.32) at follow-up (i.e. "late life"). Females represented 54.48% of the sample (n = 3,897) and the average time between the baseline and MRI visit was 7.55 years. The percentage of participants reporting weekly participation at mid-life was as follows: leisure time computer use (n = 6,340, 88.65%), visiting friends and family (n = 5,750, 80.4%), going to the pub or a social club (n = 2,540, 35.51%), undertaking religious activities (n = 1,723, 24.09%) and attending educational classes (n = 903, 12.63%) and going to a sports club/gym (n = 3,852, 50.08%). A substantially fewer number of individuals had completed all of the cognitive measures at follow-up and were therefore analysed as a sub-set (n =1,734) of the main sample.

Table 5.1 Participant characteristics.

		Range
N. of participants	7152	
Duration between baseline and MRI scan (years)	7.55 years	4.29 – 10.85
Demographics		
Age at baseline	56.39 ± 7.31	40 – 70
Age at MRI scan	63.94 ± 7.32	46 – 80
N. of females (%)	3,897 (54.48)	
Most common qualification earned (N.; %)	University/ college degree (3,624; 50.67)	
Most common occupational status (N.; %)	Professional occupations (2,290; 32.02)	
Activities		
N (%) reporting weekly participation in:	**Mid-life**	**Late life**
Leisure-time computer use	6,340 (88.65)	6,778 (94.77)
Visiting friends and family	5,750 (80.40)	5,874 (82.13)
Going to the pub or social club	2,540 (35.51)	2,513 (35.14)
Undertaking religious activities	1,723 (24.09)	1,770 (24.75)
Attending educational courses	903 (12.63)	775 (10.84)
Going to a sports club or gym	3,852 (50.08)	3,539 (49.48)
Health and Lifestyle		
BMI (kg/m^2)	26.4 ± 4.01	16.14 – 55.07
BP (MAP)	99.57 ± 11.84	60 – 152.83
Alcohol (frequency/ week)	3.41 ± 1.35	0 – 5
N (%) with ICD-10 diagnosis of Depression/Anxiety	51 (0.71)	
Sleep duration (hours/night)	9.21 ± 0.93	2 – 13
Scanner		
N. of participants scanned at Reading site (%)	6,126 (85.65)	
Relative head motion	0.12 ± 0.06	0.03 – 1.39
Structural MRI measures		
Total GM (volume, mm^3)	613,301.98 ± 54,614.44	443,926 – 832,927
WM (volume, mm^3)	547,421.16 ± 61,214.82	362,561 – 804,641
CSF (volume, mm^3)	36,479.39 ± 17,032.15	7,613.27 – 157,075
WM hyperintensities (volume, mm^3)	48,17.01 ± 6,150.75	30 – 86,534
Cognitive function (n = 1734)		
Fluid intelligence score	7.04 ± 1.93	1 – 13
Alphanumeric trail making (seconds)	52.28 ± 21.30	21.1 – 242.1
Numeric trail making (seconds)	21.5 ± 7.56	9.4 – 112.9
Pairs matching test (total errors)	6.52 ± 3.35	0 – 28
Simple reaction time (seconds)	0.59 ± 0.1	0.37 – 1.34
N. of correct symbol-digit matches	19.74 ± 5.14	2 – 36
Backward digit span score	6.91 ± 1.22	2 – 12
Prospective memory score (N. % correct)	1,510 (87.08%)	

Note: Values are Mean ± Standard deviation.
Abbreviations- BMI = Body mass index; BP = Blood pressure; CSF = Cerebrospinal fluid; GM = Grey matter; ICD = International Classification of Diseases; MAP = Mean arterial pressure; MRI = Magnetic resonance imaging; N = number; WM = White matter.

5.3.2 Comparisons of Included and Excluded Participants

Welch's t-test was performed as the variances of all continuous variables significantly differed between excluded and included individuals (Levene's test $p < 0.05$), Compared to excluded individuals, participants included in the main MRI analysis were on average, older, more likely to be female, more educated, from a higher occupational grade and had a lower BMI (all FDR q-values < 0.01). They also consumed, on average, more alcohol, lived with fewer people and slept longer hours per night (all FDR q-values < 0.01). Included individuals had less relative head motion (FDR q-value < 0.01) than those excluded. There were no differences in BP, head size or the number of depressed/anxious individuals (FDR q-value > 0.01; Appendix 5.5).

5.3.3 Associations Between Activities, Brain Structure, Functional Connectivity and Cognitive Function

In order to maintain a similar format to the previous chapters, the results involving cognitive function are first presented (n = 1,734), followed by the MRI results (n = 7,158).

5.3.3.1 Cognitive Function

5.3.3.1.1 Mid-life Activity Levels

Adjusting for sociodemographic factors (i.e. Model 1) and applying FDR corrections for multiple comparisons, only mid-life computer use was found to be associated with faster response times on the numeric path trail (B = -0.04, SE = 0.01, β = -0.11, $p_{uncorrected} <$ 0.01, FDR q < 0.01) and a greater log odd of responding correctly on the prospective memory task (OR = 2.07, 95% C.I. = 1.38 – 3.04, $p_{uncorrected} < 0.01$, FDR q = 0.02). When health and lifestyle variables were also co-varied for (Model 2), the relationship between weekly computer use and better numeric path trail (B = -0.04, SE = 0.01, β = -0.11, $p_{uncorrected} < 0.01$, FDR q < 0.01) and prospective memory performance remained

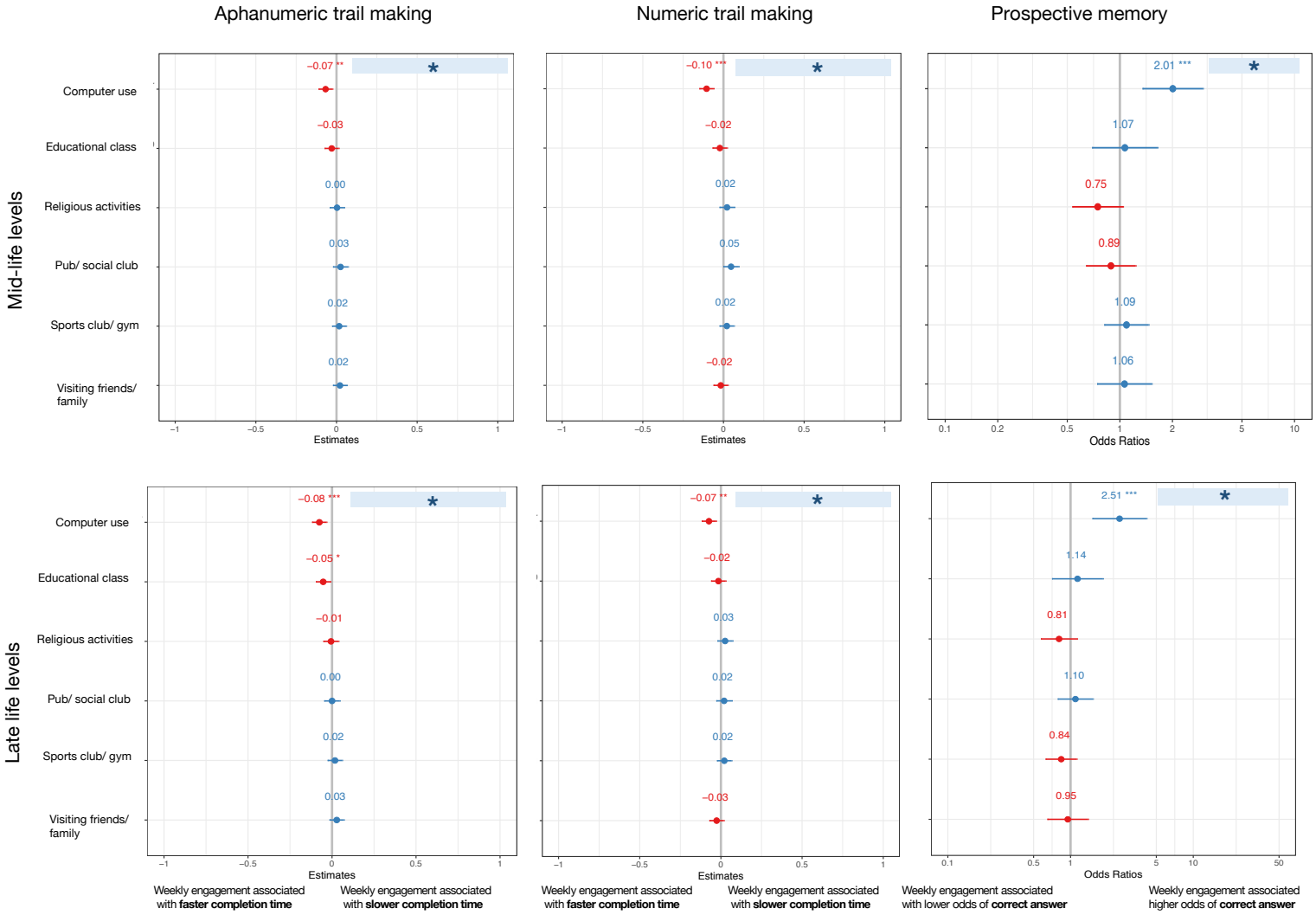
unchanged (OR = 2.07, 95% C.I. = 1.38 – 3.05, $p_{uncorrected} < 0.01$, FDR q = 0.01). An association between this activity and alphanumeric path trail performance was also detected at this stage (Model 2: B = -0.34, SE = 0.01, β = -0.11, $p_{uncorrected} < 0.01$, FDR q = 0.02). In the model adjusting for participation in all other activities (i.e. Model 3, Figure 5.2), the associations between computer use and performance on the numeric and alphanumeric path trails and prospective memory remained significant ($p < 0.05$, Appendix 5.6).

5.3.3.1.2 Late life Activity Levels

Weekly computer use during late life was associated with higher fluid intelligence scores (B = 0.69, SE = 0.2, β = 0.08, $p_{uncorrected} < 0.01$, FDR q < 0.01), faster completion of the numeric (B = -0.04, SE = 0.01, β = -0.07, $p_{uncorrected} < 0.01$, FDR q < 0.01) and alphanumeric (B = -0.05, SE = 0.01, β = -0.07, $p_{uncorrected} < 0.01$, FDR q < 0.01) trails and a higher log odds of responding correctly on the prospective memory task (OR = 2.54, 95% C.I. = 1.51 – 4.16, $p_{uncorrected} < 0.01$, FDR q = 0.01), after co-varying for variables including age, sex and educational level (i.e. Model 1). Attending an educational course in late life was also related to higher fluid intelligence scores (B = 0.44, SE = 0.15, β = 0.07, $p_{uncorrected} < 0.01$, FDR q < 0.02). In the model adjusting for health and lifestyle factors (i.e. Model 2), the relationship between late life computer use and fluid intelligence (B = 0.69, SE = 0.2, β = 0.08, $p_{uncorrected} < 0.01$, FDR q < 0.03), numeric (B = -0.04, SE = 0.01, β = -0.07, $p_{uncorrected} < 0.01$, FDR q < 0.02) and alpha numeric (B = -0.05, SE = 0.01, β = -0.07, $p_{uncorrected} < 0.01$, FDR q < 0.02) and prospective memory (OR = 2.57, 95%CI = 1.52 – 4.21, $p_{uncorrected} < 0.01$, FDR q = 0.01) performance remained significant. Associations between fluid intelligence score and attending educational courses use (B =

0.45, SE = 0.15, β = 0.07, $p_{uncorrected} < 0.01$, FDR q < 0.01) and going to the pub/social club were also detected (B = -0.29, SE = 0.1, β = -0.07, $p_{uncorrected} < 0.01$, FDR q < 0.03). When mutually adjusting for the inter-activity effects, computer use continued to associate with fluid intelligence score (FDR q = 0.01), numeric (FDR q = 0.01) and alpha numeric (FDR q = 0.02) and prospective memory score (FDR q = 0.01, Figure 5.2). Associations between fluid intelligence score and attending educational courses use (FDR q = 0.01; for details see Appendix 5.7) also remained significant.

Figure 5.2 Dot-and-whisker plots to show associations between mid-life and late life computer use and alphanumeric trail making (standardized beta coefficients), numeric trail making (standardized beta coefficients) and prospective memory performance (Odds ratio). Red values reflect negative correlations whereas blue values reflect positive correlations. Note that asterisks with a blue background reflect associations surviving FDR corrections, while a standalone asterick (*) demonstrates significant associations at $p_{uncorrected} < 0.01$. Further significant codes: ** = $p_{uncorrected} < 0.001$; *** = $p_{uncorrected} < 0.0001$.



5.3.3.2 Structural MRI

5.3.3.2.1 Mid-life Activity Levels

After adjusting for sociodemographic and imaging confounders and applying FDR corrections for multiple comparisons, we found that individuals who used the computer for leisure on a weekly basis during mid-life had greater volumetric measures in the left putamen, relative to individuals who used the computer less frequently (Model 1: B = 75.31, SE = 17.51, $\beta = 0.04$, $p_{uncorrected} < 0.01$, FDR q = 0.02). This association survived co-variate adjustments for health and lifestyle factors (Model 2: B = 79.05, SE = 17.51, $\beta = 0.04$, $p_{uncorrected} < 0.01$, FDR q = 0.01) and participation in other activities during mid-life (Model 3: FDR q = 0.01, Figure 5.3 – 5.4). Going to the pub or social club on a weekly basis in mid-life was also associated with lower total GM volume (Model 1: B = -2771.01, SE = 683.61, $\beta = -0.02$, $p_{uncorrected} < 0.01$, FDR q = 0.03), although this did not survive further adjustments for covariates, such as alcohol intake and sleep duration (Model 3: FDR q > 0.05; Appendix 5.8).

No associations were found between any of the other activities and cortical or sub-cortical GM volume, tract-specific FA or MD (Appendix 5.10), total WM volume or lesions, survived corrections for multiple comparisons (FDR q > 0.05).

5.3.3.2.2 Late life Activity Levels

No associations were found for any of the current activities with the MRI measures of GM (Appendix 5.9) and WM (Appendix 5.11) examined (FDR q > 0.05).

Figure 5.3 Diagram to highlight the left putamen, which was positively associated with mid-life computer use. The putamen region-of-interest (blue) is derived from the Harvard-Oxford subcortical atlas and is superimposed on a 3-dimensional MNI 152 template.

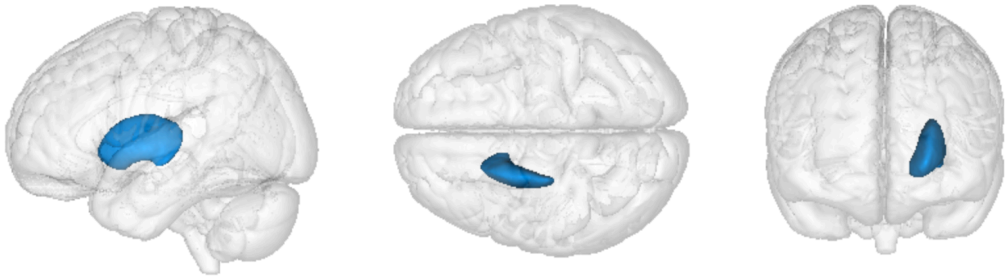
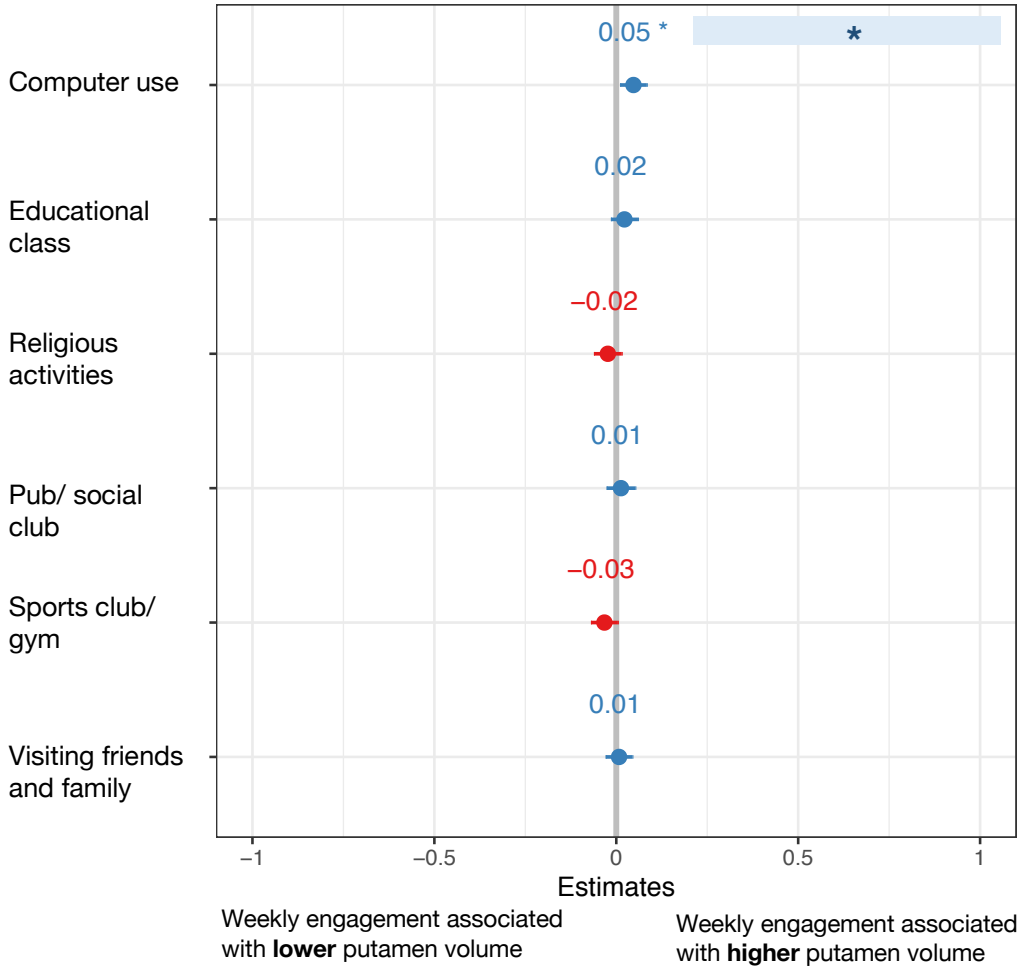


Figure 5.4 Dot-and-whisker plots of standardized beta coefficients comparing the standardized magnitude of the association between weekly computer use against all other activities. Blue values reflect positive coefficients whereas red values reflect negative associations. Note that asterisks with a blue background reflect associations that survived FDR corrections, while a standalone asterisk demonstrates significant associations at a $p_{uncorrected} < 0.01$.

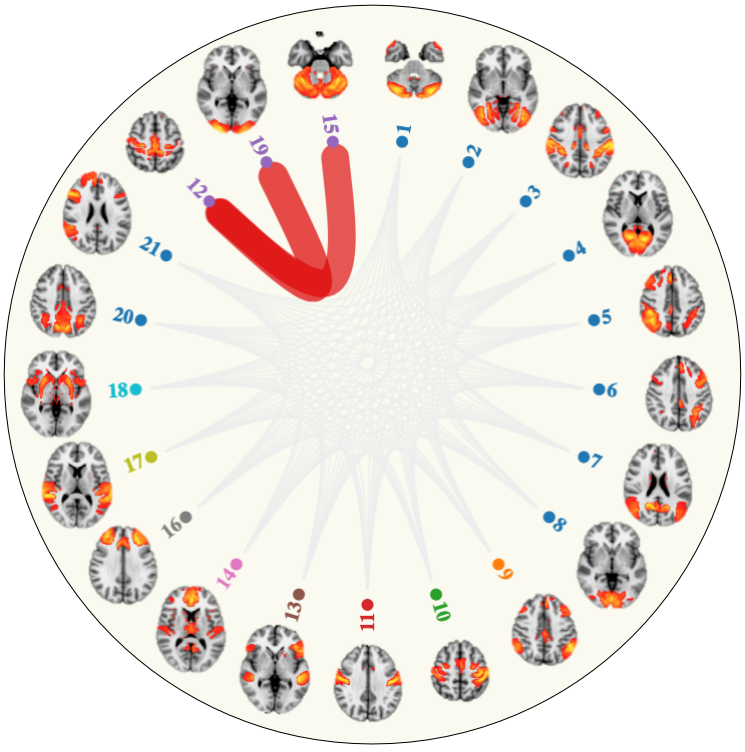


5.3.3.3 Functional MRI

5.3.3.3.1 Mid-life Activity Levels

Weekly or more frequent attendance at a sports club or gym was associated with stronger absolute connectivity between the sensorimotor network and lateral visual network (Model 1: B = 0.06, SE = 0.01, β = 0.05, $p_{uncorrected} < 0.01$, FDR q = 0.02), which was also observed after adjustments for lifestyle and health (Model 2: B = 0.06, SE = 0.01, β = 0.05, $p_{uncorrected} < 0.01$, FDR q = 0.01) and weekly participation in other activities at mid-life (Model 3: FDR q = 0.01; Figure 5.4). Similarly, stronger connectivity was also observed between the sensorimotor network and cerebellar network in individuals who went to a sports club or gym on a weekly basis, relative those who attended less frequently (Model 1: B = 0.06, SE = 0.01, β = 0.05, $p_{uncorrected} < 0.01$, FDR q = 0.03; Model 2: B = 0.06, SE = 0.01, β = 0.05, $p_{uncorrected} < 0.01$, FDR q = 0.02; Model 3: FDR q = 0.01; Figure 5.5; Appendix 5.12). Post-hoc sensitivity analyses adjusting for total GM volume did not change the significance or effect size of the associations reported (data not shown).

Figure 5.5 Mid-life sports club and gym attendance was associated with stronger connectivity (red lines) between the sensorimotor network (node 12) and lateral visual network (node 19) and cerebellar network (node 15).



5.4.3.3.2 Late life Activity Levels

There were no significant associations between current activities and connectivity strength between any of the large-scale resting-state networks (FDR $q > 0.05$; Appendix 5.13).

5.4 Discussion

This chapter presents the first known multi-modal study to comprehensively examine whether participating in various activities (during mid-life and late life) independently contribute to brain ageing. We found that weekly leisure-time computer use was related to greater putamen volume and higher performance on tests of cognition, relative to less frequent engagement. Furthermore, weekly participation in a sports club or gym correlated positively with connectivity of the sensorimotor network, although demonstrated no associations with cognition. Attending an educational course was also linked positively to fluid intelligence, but not with any of the MRI markers. We discuss the results of each of these activities in turn.

We found that individuals who used the computer for leisure on a weekly basis had more intact cognitive domains, including fluid intelligence, attention and task-switching, prospective memory and processing speed, when adjusting for sociodemographic, imaging, health and lifestyle factors, as well as participation in all other activities. Parallel associations with cognitive test performance was also observed for late life computer use. These findings are in line with the results of Tun and Lachman (2010) who examined a sample of 2,671 individuals aged between 32-84 and reported positive associations between computer use and global cognition and task-switching abilities. Our results are also consistent with a recent analysis of two cohorts suggesting that greater internet use among older adults is linked to better cognitive function (Berner et al., 2019). It is interesting to note that television-viewing, a similar activity in terms of sedentary and screen time, appears to have negative associations with cognitive function (e.g. Hoang et

al., 2016; Lindstrom et al., 2005). As discussed in Chapter 2, a key explanation for why watching the television is implicated as a risk factor for cognitive decline may be the passive nature of this activity. While computers do offer similar functionalities to televisions when it comes to watching programmes/films, they also offer comparably more, including greater exposure to novelty (e.g. reading articles online), a greater demand on psychomotor skill (through mouse use and typing) and the opportunity to engage several domains of cognition at once (e.g. attention and memory when playing computer games; Tun and Lachman, 2010). There is also a large body of literature to suggest that computerized CT may lead to improvements in trained cognitive domains, with some evidence to suggest that this may extend to untrained domains (e.g. Kueider et al., 2012; Nguyen et al., 2019). The CT literature is also supportive of a *causal* effect of cognitive stimulation on cognition. As we observed positive associations with cognition for both mid-life and late life computer use, our results may be taken to suggest that interventions designed to encourage 'active' computer use could be administered to both middle-aged and older adults. Prior to such research being undertaken, it will be important to first clarify *what* drives the associations between computer use and cognition.

It is somewhat surprising that given the extensive links with cognition, the only region to associate with mid-life computer use was GM volume in the left putamen. Classically regarded as a structure involved in movement preparation and execution (Ell et al., 2011), it is perhaps expected that an activity placing repeated strain on the motor system (via typing and mouse use) might contribute to improvements in these abilities, as indicated by faster performance on the numeric and alphanumeric trail making tests. However, comparable improvements were not found in a separate task measuring simple reaction time, which suggests that a faster reaction time is unlikely to explain the correlations between computer use and performance on the trail making tasks. Notably, the putamen

has more recently been implicated in non-motor functions, including executive control, working and episodic memory and category fluency (Ell et al., 2011). It may, however, be premature to conclude that computer use selectively contributes to the putamen and has no relationship with either functional or structural connectivity. This is because a number of trends were observed with other measures of regional grey matter, tract-average FA and MD and functional connectivity (at a $p_{uncorrected} < 0.05$ level), see Appendices 5.8-5.13), prior to FDR corrections. These trends will of course need to be independently validated by future studies to determine whether they reflect genuine associations, or are simply a Type I errors brought about by a large sample size (Miller et al., 2016). If the former is true, then our FDR corrected results may only reflect the 'tip of the iceburg'.

Another key finding of this study was that going to the gym or attending a sports club, on a weekly basis correlated with functional connectivity between large-scale resting-state networks in late life. Specifically, mid-life participation in this activity was related to greater absolute connectivity of the sensorimotor network with the cerebellar and lateral visual network. Similar activation patterns at rest and during task execution indicate that both the sensorimotor and cerebellar networks may play a role in motor tasks (Smith et al., 2009), potentially interacting with one another to support motor behaviour. This is supported by the observation that subdivisions of the cerebellum are detected within the sensorimotor network (Dobromyslin et al., 2012; Habas et al., 2009). Our study also observed a similar pattern of results, finding that the sensorimotor network component of interest featured several clusters within the cerebellum, including the vermis VIIa, bilateral crus I and bilateral V (as defined by the Diedrichsen cerebellar atlas (http://www.diedrichsenlab.org/imaging/propatlas.htm in FSLeyes). It was interesting to find that this network also had greater connectivity strength with the lateral visual network in individuals reporting weekly sports club/gym attendance, potentially suggesting

enhanced visual-motor coupling. Indeed, different types of physical activities rely on visual information as a way of regulating and adapting current behaviour (Mallek et al., 2017). An individual on a run, for example, needs to continually monitor their surroundings, identify and, if required, avoid obstacles such as traffic or pedestrians. Seed-based approaches also suggest that there is increased connectivity relative to controls between regions involved in the visual network (e.g. primary sensory area, secondary visual cortices) and sensorimotor network (e.g. premotor cortex; primary motor area) after a 13-week physical activity intervention, (Demirakca et al., 2016). Increases in connectivity strength *between* resting-state networks in an ageing sample can, however, be difficult to interpret. For instance, the results of Cassady and colleagues (2019) suggest that older adults may have less segregated sensorimotor motor networks (i.e. lower within-network connectivity and higher between-network connectivity) when compared to younger adults, with these increases in connectivity linked to poorer sensorimotor behaviour (as measured by, for example, reaction time, dexterity, grip strength and timed walking tests). If this were, however, the case, we would expect to find gym/sports club attendance correlating with poorer performance on our measures of reaction time. As we did not find any neuropsychological correlates with this activity, our results may instead indicate that these observed increases in sensorimotor connectivity do not translate to observable behavioural differences. Building on these findings, a future direction may be to examine a comprehensive battery of gait and mobility tests to better assess whether (a) there are behavioural correlates when examining multiple domains of mobility and (b) whether sensorimotor network connectivity mediates these associations. Frailty – previously linked to sports club attendance (Watts et al., 2017) – is also a potentially meaningful endpoint that could be examined.

Our final observation was that educational class attendance during late life correlated with

higher fluid intelligence scores. These results resonate with a growing body of evidence in favour of life-long learning, and it's contributions to maintaining cognitive health (Hatch et al., 2007; Matyas et al., 2019). Notably, we did not identify similar associations with mid-life educational class attendance. The disparity in results may be explained if it assumed that the 'effects' of attending a class once a week are short-term, suggesting that this activity may need to be continually engaged in, in order for the cognitive improvements to be detected. Alternatively, this activity may only have an impact after age-related cognitive deficits begin to manifest. Given that we are demonstrating a cross-sectional association, our study may simply be detecting a self-selection bias, such that those who are more cognitively intact choose to attend these educational courses. Reassuringly, results from the Baltimore Experience Corps trail provide evidence that enrolling older adults in an 30-hour intensive program (characterized by lecture, exercises, and interacting with children) based in elementary schools leads to improvements in cognition (Carlson et al., 2008). Several papers based on this study, also point towards differences in BOLD signal (Carlson et al., 2009), and cortical GM volume (Carlson et al., 2015). In contrast, no associations with functional connectivity, GM or WM microstructure were identified with the UK Biobank data. This is likely because we were only able to examine *weekly* course attendance, without the sensitivity to distinguish between individuals who attend only once a week, to those who attend more frequently. As the Experience Corps intervention was designed to be intensive, it is feasible to postulate that brain changes would only be detectable in the latter group. Overall, our findings still have practical implications, emphasizing the importance of educational courses designed for older adults. In the UK, the University of the Third Age offers a variety of lectures for semi-retired or retired people (https://www.u3a.org.uk/). We are, however, aware that only 11% of our sample reported that they attended any such courses in their old age. Free, accessible and regular courses based in the community (e.g. town hall, local schools or cafes) may be more far-reaching,

targeting individuals who may prefer 'casual' learning experiences.

None of the other activities (i.e. visiting friends and family, going to the pub or social clubs, undertaking religious activities), measured in either mid-life or late life, were associated with markers of GM, WM microstructure, functional connectivity or cognitive function, after applying FDR corrections. While prior meta-analytic investigations have identified associations with brain structure (Anatürk et al., 2018) and cognition (Kuiper et al., 2016) when activities (e.g. going to the pub or visiting friends and family) are combined into composite scores, our results suggest that comparatively speaking, they do not appear to uniquely contribute to brain health in early late life. It is also important to highlight that weekly pub/social club attendance had negative associations with fluid intelligence (β = -0.07) prior to controlling for participation in other activities. Given that we have demonstrated that there are inter-activity differences in brain-cognition associations, our results indicate that if the statistical power allows for it, future studies should preferentially examine how different activities contribute to the ageing brain, rather than relying on composite measures of social/cognitive activity levels. Overall, our study results are informative for both clinicians and researchers planning an RCT study, as it highlights specific cognitive (i.e. using the computer, attending educational courses) and physical activities (i.e. attending a sports club/gym) that may have a greater role to play in maintaining neural and cognitive health than other types of leisure activities. Such studies may be valuable for updating current recommendations (e.g. https://www.nia.nih.gov/health/cognitive-health-and-older-adults) and guidelines (https://www.who.int/mental_health/neurology/dementia/guidelines_risk_reduction/en/) on how best to preserve cognition in older adults.

5.5 Strengths and Limitations

The core strength of this study is that is based on longitudinal data (average follow-up period = 8 years) provided by a large cohort of middle-aged and older adults. Given that UK Biobank had 2 waves of information on activity levels available, it also provides insights into the neural and cognitive correlates of mid-life and late life activities, without relying on retrospective assessments of mid-life activity levels (reviewed in Chapter 2 with the disadvantages discussed in Gow et al., 2017). Furthermore, stringent multiple comparison corrections were applied to minimize spurious findings, as larger studies are generally at a greater risk of identifying significant-but-meaningless associations (Miller et al., 2016). Additionally, it is interesting that we were still able to observe associations with neural and cognitive measures, despite our use of a relatively insensitive scale, which saw participants being divided into either weekly or less frequent engagers. A slight disadvantage of this approach is that some variables were dichotomized from more fine-grained scales (hours/ week or frequency/ week). This led to an inevitable loss of information but was deemed a necessary step to ensure that differences in the response scale for the activities assessed did not account for differences in the results between activities. The binary nature of the variables and only two time points of activities available further prevent any trajectory analyses from being conducted (as done in Chapter 4), which may have revealed further insights into how changes in activities over time relate to brain markers. Another outstanding question is whether we would see more profound brain changes if the average hours dedicated to a given activity each day had been examined, rather than weekly engagement levels. Another important point is that we were only able to examine six activities available in Biobank. Other common activities, such as reading (Paillard-Borg et al., 2009) were not assessed here. This study therefore represents an initial step towards characterizing activity-specific associations with the brain better but is by no means exhaustive. Further work is required to parse out the specific set of activities that have greater implications for brain ageing, generating evidence that will help improve our

design of RCTs and retirement programmes in order to ensure that the most promising activities are targeted.

A repeatedly highlighted point of discussion in this thesis is that this study is limited by its entirely correlational design. Although we have been comprehensive in the co-variates examined, due to the non-randomized nature of the sample, we are unable to rule out reverse causation (see example regarding educational course attendance) or residual confounding by a third unaccounted for variable. As an example of the latter, it may be the case that individuals who frequently use the computer are simply more accustomed to interacting with technology and therefore also perform better on the computerized tests of cognition. Cohort effects may alternatively explain our results. For example, while older individuals who are now fully engaged with technology may gain cognitive benefits, the same effects might not be observed in 20 years' time as it becomes more common for individuals to become computer literate from a young age. On the topic of computer use, the item assessing this activity was also too general to pinpoint which *particular aspect* of using a computer may be most relevant for brain ageing. Some studies point towards exploration in internet usage (Berner et al., 2019) with others suggesting psychomotor skills used in computer games (Schultz et al., 2015), as contributing factors towards cognitive function or underlying brain structure. Motivated by these findings, we conducted post-hoc exploratory analyses to investigate whether playing computer games (at midlife; data available for 7140 individuals) accounted for the relationship between leisure-time computer use and putamen volume. Linear regression analyses continued to find an association between computer use and putamen volume, with minimal change to the magnitude of this relationship ($\beta = 0.04$, $p_{uncorrected} < 0.01$, FDR $q = 0.02$). When it came to cognitive function, only the relationship with mid-life computer use and numeric path trail performance and prospective memory survived FDR corrections (FDR q-values < 0.05).

This would suggest that while computer gaming may account for some of the associations between computer use and cognition, it did not completely account for the link with putamen volume. Such findings call for more comprehensive assessments of computer use, to parse out the driving force behind these associations. A final note is that there were significant differences between individuals included in the sample to those excluded, with those included generally being older, more educated and from a higher occupational grade, being more likely to be female and differing in their lifestyle (e.g. alcohol, sleep duration) and health (BMI) parameters. These comparisons resonate with the results of previous chapters (3-4) and an investigation of the larger Biobank cohort (drawing comparisons with the British general population; Fry et al., 2017). Individuals included in these types of analyses are generally healthier than those excluded. This would suggest that our results are most applicable to those who share similar characteristics to our sample and may not equally generalize to all middle- and older-aged adults.

5.6 Conclusions

Motivated by the limited associations found between leisure activities and underlying brain structure and functional connectivity in the Whitehall analyses (Chapters 3-4), the present chapter aimed to examine how *individual activities* relate to these MRI markers, in constrast to the composite measures of leisure activities used in the preceeding chapters. We found that computer use during mid-life correlated with larger volumes of the left putamen and multiple domains of cognition. The links with cognition were also largely replicated for late life computer use. Furthermore, mid-life sports club/gym attendance was linked to sensorimotor connectivity, but not to cognitive performance. Attending educational classes in old age conversely held associations specific to fluid intelligence performance, with no other activities harbouring links with either cognitive domains, brain structure or functional connectivity. Overall, this study suggests several activities that may be of interest

to future RCTs, with the concluding message to ensure that the development of *multi-modal* interventions is prioritized, due to the small effects of activities that are reported here.

CHAPTER 6

Conclusions and Future Directions

Contents

6.1 Revisiting the aims of this thesis 188

6.2 Conclusions 190

6.2.1 Activities Are Linked with Late Life Cognition 190

6.2.2 Minimal Links Between Activities and MRI Indices 193

6.3 Final methodological considerations 195

6.3.1 Study Design and Directionality 195

6.3.2 Measurements of Leisure Activities 197

6.3.3 Definitions of Leisure Activities 198

6.3.4 Demographics and Generalizability 202

6.4 Suggestions for Further Works 203

6.5 Concluding Remarks 204

6.1 Revisiting the Aims of This Thesis

The main objective of this thesis was to investigate whether cognitive and social activities associate with measures of cognitive function, brain structure and functional connectivity in late life. Each of the individual chapters have taken a different approach to addressing this overarching objective, beginning with Chapter 2, which aimed to pool existing evidence to clarify what is known about the relationship between leisure activities and brain health in a systematic review and meta-analysis. The combined results of previous studies suggested that participating in both cognitive *and* social activities associated positively with whole-brain measures of WM volume and hippocampal volume and with fewer WM lesions. Correlations with regional GM, spanning across all lobes, were also identified. Chapter 3 aimed to address one of the important gaps highlighted in the review, by examining whether *late life* social and cognitive activities related to cognitive function and

MRI markers of brain structure *and* functional connectivity. Here, only cognitive activities held associations with global and domain-specific (i.e. executive function) cognition. While social activities were not linked to cognition, they uniquely associated with an MRI measure, i.e. global GM volume. Chapter 4 sought to move beyond the cross-sectional design of the previous chapter and the literature review of Chapter 2, to investigate whether *longitudinal changes in activities* between mid-life and late life, separated into distinct trajectories defined by data-driven approaches, contribute to brain structure and function. This chapter revealed that the *level* of cognitive activities was linked in a non-specific way with cognition (i.e. global, executive function, memory and processing speed) with social activities demonstrating domain-specific effects (executive function). It was additionally found that social activity trajectories with an initial increase (during mid-life), followed by a levelling off/decrease in later life were related to *poorer* cognition, whereas cognitive activity levels following this pattern were related to *better* performance on cognitive tests. We further identified links between social activity trajectories and sensorimotor functional connectivity and a small cluster within this network. Cognitive activities trajectories, on the other hand, associated with total GM volume. Finally, Chapter 5 aimed to refine the analysis, with the aim of understanding the role of *individual* activities in brain ageing. It was evident from this chapter that not all activities are equal in their role of modifying cognitive and neural ageing, with mid-life computer use, participation in sports club or gyms, and educational class attendance being the only three activities to show any associations with such outcomes. In the following section, the main conclusions of this thesis are discussed.

6.2 Conclusions

6.2.1 Activities Are Linked With Late Life Cognition

Prior epidemiological evidence implicates a role of cognitive activity in maintaining late life cognitive function (Matyas et al., 2019). Our findings were largely in line with this body of work. Specifically, the analyses of Whitehall data revealed that late life participation was linked to higher executive function and global cognition (Chapter 3) with even more extensive links, when assessed longitudinally (Chapter 4; global cognition, executive function, memory, processing speed). Our Biobank analyses (Chapter 5) further identified that both mid-life and late life weekly computer use were significant correlates of better functioning in multiple domains of cognition, including fluid intelligence, attention and task-switching, prospective memory, and processing speed. The recent findings of Krell-Roesch et al. (2019) corroborate our observations, as they report that both mid-life and late life computer use predicted a lower risk of incident MCI, after examining this outcome in relation to different activities during these life time periods (i.e. reading books; playing games; craft activities; social activities). Late life attendance to educational classes was also highlighted in the Biobank study as a unique correlate with fluid intelligence, which if replicated, could make a strong case towards investing in programmes that encourage lifelong learning. Overall, we have largely been able to replicate the level-level associations previously identified between cognitive activities and cognition, further highlighting two activities that may have a role in maintaining late life cognition.

The literature predating our analysis of *cognitive activity trajectories* has been relatively consistent, with one multi-cohort study reporting that *increases* in cognitive activities correlate with better performance on tests of semantic knowledge, memory, language fluency and reasoning (Mitchell et al., 2012). Others have further demonstrated that, as would be expected, *declines* in this type of activity over time associates with poorer

performance on tests of cognition (Small et al., 2012). Our results were largely complimentary with these observations, finding that individuals who increased their cognitive activities during mid-life and then either maintained or reduced these levels in the subsequent years had *better* performance on tests of global cognition and sub-domains (e.g. executive function, memory, processing speed), relative to individuals who exhibited less change in their cognitive activity habits over time. While the observations of Small and colleagues (2012) suggest that any kind of decrease in cognitive activities is adverse - ours contrastingly could be taken to suggest that if an individual is intellectually engaged through their mid-life, then withdrawing from these habits at a later date may not necessarily be as harmful to cognitive health as previously thought. While only speculative, several RCT studies support the hypothesized long-term effects of cognitive training, although differences in intervention type, follow-up period and definition of maintenance complicate inter-study comparisons (Joubert and Chainay, 2018). As cognitive training and leisure activities are dissociable in their effects on cognitive abilities (Stine-Morrow et al., 2008), our results call for more research into the endurance of effects in the latter class of interventions.

Correlations spanning multiple cognitive domains have previously been reported for social activity levels (i.e. global cognition, executive function, memory; Evans et al., 2018). However, our results suggest a far more limited role of social engagement in maintaining cognitive function. For example, Chapter 3 found *no associations* between *late life levels* of social activities and our assessments of global cognition, executive function and memory in the Whitehall cohort. Chapter 5 corroborated this observation, as none of the social activities measured in late life (e.g. visiting friends and family, going to the pub or social club, participating in religious activities) held significant links to tests of cognitive function, within the UK Biobank sample. In contrast, Chapter 4 was somewhat more supportive, as

social activity levels measured several years prior to the cognitive battery linked exclusively to executive function, when the longitudinal panel data of the Whitehall study were examined. As this thesis mainly focused on social activities conducted in the public sphere (e.g. based at a club or community centre), one question that remains is whether home-based, one-to-one social activities hold differential associations with cognition. Several studies suggest that these types of social activities have comparatively stronger links with cognition compared to public/group-based activities (Bielak et al., 2014; Jopp and Hertzog, 2010). It would, therefore, be of interest for further studies to clarify whether it is this particular dimension of a social activity (private/public; group/one-to-one) moderates associations between social activity levels in late life and cognitive function.

When *changes* in social activities are the focus, a previous comparison of four studies (based in Sweden, USA and Canada) observed that increases in social activities were linked to less decline in semantic knowledge and better language fluency, reasoning and memory over time (Brown et al., 2012). Changes in one-to-one social activities have also been reported to associate positively with immediate episodic memory (Bielak et al., 2014). Our findings suggest that these prior observations may only provide part of a more complex story. Specifically, in our longitudinal analysis of Whitehall II data (Chapter 4), we found that trajectories following a steep initial increase and then a subsequent *levelling off or decrease* in social activities between mid-life and late life were associated with poorer executive function at follow-up. Collectively, the evidence is consistent with the explanation that *while* increases in social activities from an individual's baseline may contribute to better cognitive function in late life, taking on more activities than can be maintained over time could potentially lead to negative consequences for executive function. Of course, there is an urgent need to replicate and confirm the findings reported here in a larger, independent

cohort of individuals, particularly in light of the null findings reported in Chapters 2 and 5.

6.2.2 Minimal Links Between Activities and MRI Indices

The meta-analysis of published findings (Chapter 2), promisingly indicated that a lifestyle characterized by frequent involvement in cognitive *and* social activities was linked to greater global white matter volume and hippocampal volume and less volumetric measures of lesions across all white matter tracts. Our Whitehall II analyses were, however, less optimistic as they were unable to replicate the meta-analytic findings when cognitive and social activities were assessed separately. The only measure highlighted in our cross-sectional analyses (Chapter 3) was total GM volume (%ICV), which correlated positively with late life social activities, but not cognitive activities. This is in contradiction to several of the reviewed studies indicating that both activities correlated with regional GM (Arenaza-Urquijo et al., 2015; Bartrés-Faz et al., 2009; Seider et al., 2016), although not all studies agree with this narrative (Arenaza-Urquijo et al., 2016; Foubert-Samier et al., 2012; Schultz et al., 2015; Vemuri et al., 2016). Conversely, our longitudinal results (Chapter 4) highlighted links between cognitive activity trajectories and whole-brain GM volume, but not for social activity trajectories. No voxel-wise associations were found for either activity with GM volume, WM indices and resting-state functional connectivity, to survive co-variate adjustment (Chapter 3 and 4). Being the first study to examine resting-state functional connectivity, we conducted exploratory post-hoc analyses of networks outside those of immediate interest to us and found that the shape of social activity trajectories between mid-life and late life correlated negatively with sensorimotor connectivity, possibly due to the light physical exercise that accompany these activities.

One of the potential explanations for the discrepancy between our meta-analysis and Whitehall analyses were differences in the activities used to create our composite measures

of cognitive and social activities. Composite measures are also unable to clarify whether specific activities uniquely contribute to brain health. Chapter 5 appeared to supplement our understanding of activity-specific associations, identifying leisure-time computer use as an activity associated with brain structure (i.e. putamen volume), and sports club/ gym attendance as a correlate of functional connectivity (of the sensorimotor network). As only six activities were available in the UK Biobank, the next step will be to comprehensively examine whether there are other activities (e.g. reading) that reliably correlate with markers of brain health. This correlational work is likely to inform the design of interventions for RCT studies, which will be essential for confirming whether the observed correlations translate into clinically meaningful effects.

The strengths of the current work include the multiple approaches used to address the overarching question of whether leisure activities relate to brain integrity. The use of several sources of data to probe this research question is also a major advantage, including two independent prospective cohorts. We are also the first known study to investigate resting-state functional connectivity as an outcome in relation to cognitive and social activities, highlighting the sensorimotor network as one of interest for future studies. To date, there have only been a handful of neuroimaging studies that have collected repeat information about leisure activity levels, although none have exceeded more than two time points. Our Whitehall analyses (Chapter 4) therefore provide one of the most detailed characterizations of leisure activity trajectories and their relation to underlying brain structure and function, to date. The question of how best to operationalize leisure activities in practice has also been explored at length in this thesis, with a detailed discussion to follow.

We next discuss our work in the context of several methodological themes, as initially done in our systematic review and meta-analysis. Accordingly, several directions for further work are then proposed.

6.3 Final Methodological Considerations

6.3.1 Study Design and Directionality

A crucial design feature of both the Whitehall and Biobank analyses was that only a single time point of MRI was used, as no repeat measures were made available. Acquiring only a single assessment of MRI has been a trend observed more generally in the ageing field (Anatürk et al., 2018), no doubt due to the financial and time constraints tied to repeatedly administering this method to a large cohort of individuals and the fast development of new imaging hardware and software. This also represents a major limitation of not only the work described here, but of the wider literature. Ultimately, a single session of MRI may be insufficient to assess hypotheses that concern the potential associations shared between leisure activities and *age-associated brain changes*. As it stands, most studies in the field (ours included) have largely examined leisure activities in relation to *inter-individual differences* in brain integrity, which provides no insight into whether the brains of individuals with low cognitive/social activity levels *age at a greater rate* than individuals with high cognitive/social activity levels (i.e. *differential preservatio*n), as we would predict, or whether differences in brain structure/functional connectivity reflect *pre-existing differences* between individuals that have been maintained across the life span (i.e. *preserved differentiation,* Salthouse, 2006). This issue is further compounded by the absence of randomization inherent in observational studies, leaving a body of work that may very well be explained by reverse causation.

To address our concerns, there needs to be a dedicated shift in the field towards longitudinal MRI designs that can measure *intra-individual* changes in brain ageing directly, allowing individuals to serve as their own baseline controls. Such studies would go a long

way towards clarifying whether the lack of associations reported here between activities and brain measures are a genuine observation or an artefact attributable to the use of cross-sectional MRI. The results of Köhncke and colleages (2016) are informative when considering the potential differences between cross-sectional and longitudinal MRI, as these authors found no link between *level* of social activities and *levels* of FA and MD in the corticospinal tract but observed associations between *changes* in social activity levels with *changes* in these DTI metrics. Only after a number of studies have used longitudinal structural, diffusion tensor and resting-state functional MRI to delineate the relationship between leisure activities to *age-related brain changes*, it may be sensible to plan RCTs with repeat MRI performed to evaluate the causal effect of leisure activities on the ageing brain.

Another important consideration on study design concerns the MRI modalities that were used. We should first emphasize that throughout the empirical studies of this thesis, a comprehensive multi-modal design was used, and our selection of modalities was informed by prior evidence. Given that it remains unclear whether there are particular neural mechanisms underlying the observed activity-cognition associations in our Whitehall II analyses, it may be the case that other mechanisms not investigated are involved. For example, PET or SPECT imaging can be used to assess biomarkers of Alzheimer's disease, potentially revealing further insights into these associations of interest. A large body of evidence suggests that leisure activities relate to beta amyloid deposition, hypometabolism and perfusion deficits, in both healthy adults and dementia patients (Arenaza-Urquijo et al., 2015). These studies are most informative in understanding whether leisure activities directly relate to **(a)** pathological processes associated with Alzheimer's Disease, rather than the **(b)** brain's capacity to tolerate (i.e. brain/cognitive reserve) these changes. Overall, well-powered studies that are able to examine both **(a)** and **(b)** may be the most

fruitful in determining the underlying mediators of the links between activities and cognition.

6.3.2 Measurements of Leisure Activities

The quality of the assessment tools employed in our respective Whitehall and Biobank analyses are an important factor to consider when interpreting the results of these chapters. As observed for prior studies (Anatürk et al., 2018), leisure activities were almost exclusively measured by study-specific questionnaires, with the variety, number and type of engagement (e.g. frequency versus duration) of activities varying between surveys. The only chapter exempt from this pattern was Chapter 2, which instead focused on the CHAMPS questionnaire. Although a psychometrically validated tool that has been used by related studies (Seider et al., 2016) – the CHAMPS was not specifically designed to assess cognitive or social activities. These activities were rather included to serve as filler items in order to minimize the risk of socially desirable responses on physically demanding activities (Stewart et al., 2001). Although the case has already been made for using validated questionnaires (Anatürk et al., 2018), it is recommended that future authors prioritize those that are *specifically designed* to test cognitive and social activities (e.g. CAS; Wilson et al., 2003, 2005). Inconsistencies in the questionnaires examined between chapters also consequentially introduced differences in the number and variety of activities assessed, ranging from 6 (Biobank) to 41 (Chapter 3: Whitehall). Based on the present work, we propose that future studies should strive to examine a range of activities common to older adults, as well as those less common – a point that is emphasized in the following paragraph. We also note that there was substantial heterogeneity in the granularity of the scales employed. For example, duration was examined in Chapter 3, while frequency was measured in Chapters 4 – 5. As duration may be a more informative and direct index of activity participation than frequency, we suggest that questionnaires examining the former

be preferentially selected, as it could improve the precision of current estimates on the size of effects of interest. Although unlikely, we cannot exclude the possibility that these stated discrepancies in assessment tools, number of activities and precision of scales underlie the inconsistencies in results found between chapters.

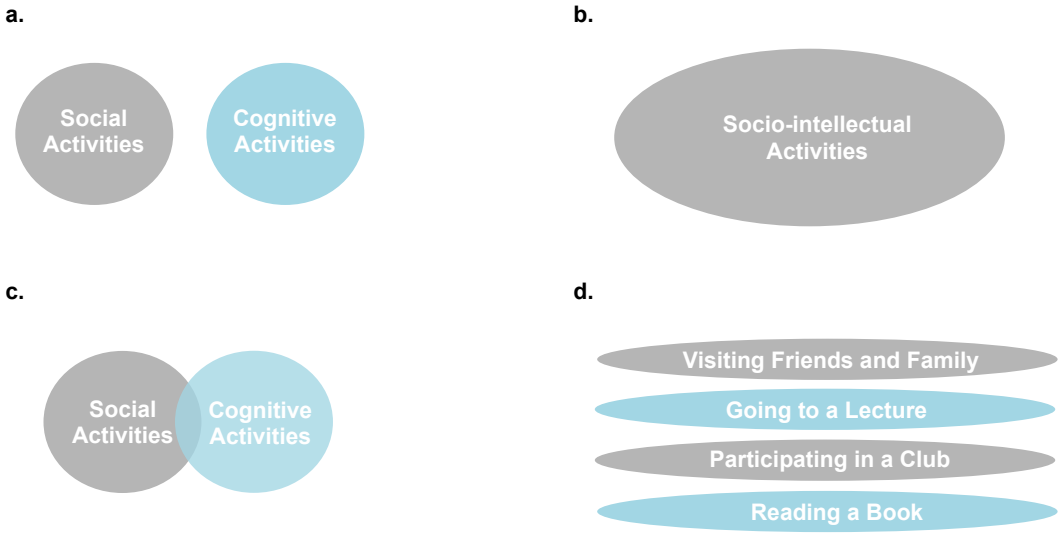
Regarding the range of leisure activities assessed, it is perhaps unsurprising that the activities assessed were largely orientated towards Western older adults. Yet new insights may be gained by moving beyond a Western-centric framework. For example, *Baduk* (*Go* in Japanese and *Weiqi* in Chinese) is a Korean board game well known in East Asia (Jung et al., 2013) that appears to hold promise for the ageing brain. In a small sample of young adults, (Jung and colleagues (2013) report that young experts in Baduk exhibited differences GM volume in subcortical structures (increases in amygdala volume; decreases in nucleus accumbens volume) and functional connectivity of these substructures with the frontal cortex. Differences in WM between Baduk experts and non-experts have also previously been documented (Lee et al., 2010). As both studies were conducted in young adults, the next step will be to characterize differences between older adults with Baduk expertise relative to those who are not. Overall, expanding the variety of activities examined by adopting a more international framework into future research may pave the way for novel insights, and ultimately provide a better understanding into the particular activities that can be integrated into retirement programmes and in a clinical setting, recommended to patients.

6.3.3 Definitions of Leisure Activities

In response to inconsistencies in how the literature has previously defined cognitive and social activities, one of the key methodological aims of this thesis was to improve the way in which leisure activities were operationalized, in practice. Revisiting Chapter 2's diagram that provides an overview of the different methods used to measure leisure activities

(Figure 6.1), it may be apparent that this thesis has employed and assessed each of the approaches described, reflecting along the way on their individual strengths and limitations. To summarize these efforts, we first employed the two most commonly used approaches to define cognitive and social activities (Figure 6.1.a. and 6.1.b; Chapter 2: meta-analysis), which involved either treating them as mutually exclusive constructs or otherwise combining scores on these activities in circumstances where a lack of data prevented us from examining independent effects. Although these methods were useful as an initial probe into the associations of interest, by the end of Chapter 2 it was clear that a given activity could concurrently possess high cognitive and social demands (e.g. playing pool), and these demands are undeniably linked. Treating them as one and the same (6.1.b.) was not an optimal solution to the problems held by the mutually exclusive approach (6.1.a.), as it precluded any conclusions being drawn about the independent contributions of these activity sub-types.

Figure 6.1 Revisiting the methods used in the literature to probe the relationship between activities and the ageing brain.



Chapters 3 and 4 aimed to take on an arguably more 'real world' approach compared to Chapter 2, by operationalizing cognitive and social activities as inter-linked or overlapping constructs (6.1.c.), and therefore allowing a given activity to have simultaneous demands in both cognitive and social activities. This would mean that a given activity could feature in composite indices representing both constructs, with a weighting assigned to it (i.e. low/moderate/high demand) to determine its relative contribution to the overall score. Although this approach overcame several of the core issues of Chapter 3, it also carried its own limitations. For instance, the demand weightings for each activity were decided upon by only three raters. While there was high agreement among these individuals in their ratings, we cannot rule out that an independent trio of raters would ascribe different demand ratings to the same set of activities. This issue can be overcome by asking a larger, more representative sample of older individuals to decide on the demand of each leisure activity. Indeed, this has previously been done in a sample of older adults (Köhncke et al., 2016) and we note that their ratings showed reasonable correspondence with our own. The sample did, however, consist of substantially older individuals (n = 41; mean age =

82.5). Hence, it is important that these ratings are replicated in an independent sample of young-old and old-old older adults. A less easily resolved issue relates to the *composite* nature of the three approaches discussed thus far.

Composite scores are useful in addressing research questions about the neural correlates of a set of activities that share a common trait (that they are socially demanding), although run the risk of masking important activity-specific effects. Consider a scenario where a researcher devises a cognitive activity index from a questionnaire containing items on television viewing, reading a book, among other activities. While television viewing appears to be a detriment for cognition (e.g. Lindstrom et al., 2005), reading is a presumed protective factor (Krell-Roesch et al., 2019). With opposing effects that are likely to cancel each other out, the use of a composite score in this case could lead to the researcher incorrectly concluding that no association exists between cognitive activities and cognition. With this in mind, Chapter 5 sought to break away from this trend to instead evaluate whether specific activities individually contributed to brain health (6.1.c). It was demonstrated that the links between individual activities and MRI markers are heterogenous, suggesting that an approach sensitive to the effects of individual activities is warranted. The added value of this method is that it may also pinpoint specific activities that could be targeted by RCTs designed to promote brain health in late life.

Overall, this thesis has demonstrated that the field of ageing research should retire mutually exclusive (6.1.a.) or non-specific (6.1.b.) definitions of cognitive and social activities. In the instance where a neuroimaging study uses a small sample size (and a composite leisure activity score is deemed essential), authors should consider approaches that allow a degree of relatedness between constructs, as demonstrated here (6.1.c.). Given the recent rise of sizeable and accessible sources of neuroimaging data (e.g. Lifebrain consortium; Walhovd et al., 2018), we would recommend that future researchers make use of large-scale data to

the fullest extent, by focusing on research questions that are most relevant for the development of RCTs – namely, the neural correlates of specific activities.

6.3.3 Demographics and Generalizability

A consistent observation of the review chapter was a trend towards healthier and more cognitively intact individuals being retained for analysis across studies, while those with a poorer health and cognitive profile systematically excluded. Our Whitehall and Biobank chapters are not exempt from this pattern as, for example, included individuals were on average younger and scored higher on the MoCA in the Whitehall sample. Although attrition and enrichment of more resilient individuals will inevitably occur for any longitudinal study (Caruana et al., 2015), selective drop-out (i.e. of individuals with ill health) may call into question to generalizability of the effects reported here (Delgado-Rodriguez, 2004). For example, a healthier-than-average sample could lead to effect sizes being under-estimated and in more extreme cases, associations of interest being potentially missed. Future studies should bear this in mind in planning to ensure that data from a sufficiently large sample is collected to prevent an underpowered analysis and that protocols are in place to minimize attrition from groups of interest (e.g. providing free transportation to participants or home assessment).

While a typically overlooked limitation, a no less important point is that the work described here is exclusively based on Western samples. For example, the studies reviewed in Chapter 2 were all undertaken in either the USA, UK, Europe or Australia. Moreover, both the Whitehall and Biobank samples used in this thesis are cohort studies based in the UK. An absence of diversity is a long-standing and much debated issue in health science (Adair et al., 2002; Bauserman, 1997; Pollet and Saxton, 2019). A poor representation of the international community also predictability restricts how generalizable our inferences can be, for example to older adults residing in Turkey, India, or Russia (to name a few). We

therefore strongly recommend that future authors consider using data provided by studies based in under-represented countries, with one future study of interest being the Harmonised Diagnostic Assessment of Dementia for the Longitudinal Aging Study in India (LASI-DAD; Lee et al., 2019). Future authors may take interest in the Gateway to Global Aging Data (https://g2aging.org/) platform, where they can apply to access data collected from different regions across the globe.

6.4 Suggestions for Further Work

In our discussion of methodological themes to arise from the present work, we have put forward a number of avenues of interest for future studies to pursue. To summarize, we have suggested that an *area of priority* is to clarify whether leisure activities relate to underlying age-related structural/functional changes by means of longitudinal MRI, to explore whether current cross-sectional findings reflect *preserved differentiation* or *differential preservation.* Our work also demonstrates the empirical contributions that studying *activity trajectories* and *individual activities* may bring to the field, beyond cross-sectional composite measures of activities, respectively. Another area of interest is to expand beyond the modalities examined here, such as integrating PET or SPECT imaging to evaluate whether these methods better delineate the underlying neural mechanisms that potentially moderate or mediate the link between activities and cognition. We have recommended that future work also strives towards maintain consistency in the questionnaires used to probe activity levels, ensure that a wide range of activities are examined (beyond those that are common to Western countries and also emphasize the added value of using fine grained scale. An international approach in this area is clearly warranted, with future works also prioritizing data collected outside of the UK, Europe and the US.

Finally, it is important to note that all of the reported effect sizes presented here imply only weak associations between activities and cognition, pointing towards the use of multi-domain interventions to successfully promote cognitive health in old age.

6.5 Concluding Remarks

Overall, this thesis presents a multi-modal examination into the relationship between leisure activities and the ageing brain. We conclude that (1) cognitive activities appear to have more far reaching links with cognition (with computer use and educational classes particularly promising), whereas mid-life, but not late life social activities harbour weaker, domain-specific associations. (2) Although associations with underlying neural substrates were scarce, we suggest that this may have been due to the use of cross-sectional MRI or absence of potentially more sensitive to other imaging modalities (e.g. PET), a caveat that can be addressed by future studies. Finally, (3) composite measures of leisure activities may inadvertently confound experimental results, and we have therefore suggested that the field, as a whole, refine its focus on activity-specific effects, which may hold more valuable information for the design of RCT programmes.

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Appendices

Contents

Chapter 2 Appendices 231
Chapter 3 Appendices 232
Chapter 4 Appendices 242
Chapter 5 Appendices 258

Chapter 2 Appendices

Appendix 2.1 Search criteria for MEDLINE.

1. *Social Behavior/

2. Cognitive Activity.mp.

3. exp Leisure Activities/

4. lifestyle factors.mp.

5. 1 or 2 or 3 or 4

6. exp Magnetic Resonance Imaging/

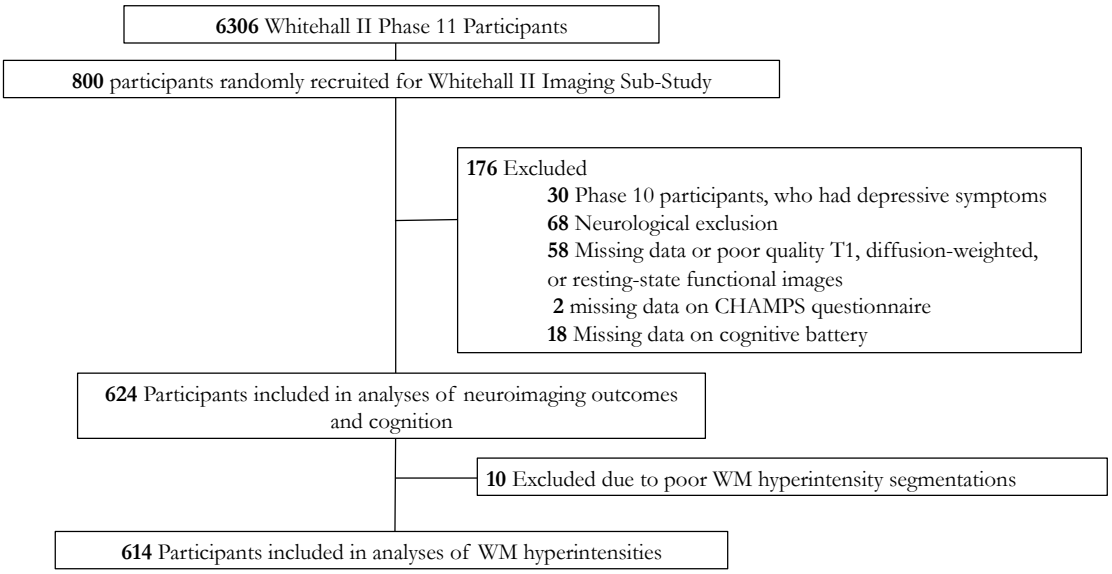
7. exp Brain/

8. 5 and 6 and 7

9. limit 8 to (English language and humans, “all aged (65 and over)” and journal article)

Chapter 3 Appendices

Appendix 3.1 A flow chart of the stages of participant exclusion.



Abbreviations- CHAMPS = Community Healthy Activities Model Program for Seniors; WM = White matter.

Appendix 3.2 Cognitive and social demand ratings for the CHAMPS (Stewart et al., 2001) questionnaire items.

	Cognitive Demand Rating	Social Demand Rating
1. Visit with friends or family? (Other than those you live with)	Medium	High
2. Go to a community or day centre?	Medium	High
3. Do volunteer work?	High	High
4. Attend church or take part in church activities?	Medium	High
5. Attend other club or group meetings?	Medium	High
6. Use a computer?	High	Low
7. Dance (such as square, folk, line, ballroom)? Do not count aerobic dance here.	Medium	High
8. Do woodworking, needlework, drawing, or other arts or crafts?	Medium	Low
9. Play golf, carrying or pulling your equipment? Count walking time only.	Low	Medium
10. Play golf, riding a cart? Count walking time only.	Low	Medium
11. Attend a concert, movie, lecture or sport event?	High	Medium
12. Play cards, bingo, or board games with other people?	High	High
13. Play snooker, pool or billiards?	Medium	High
14. Play singles tennis? Do not count doubles.	Low	High
15. Play doubles tennis? Do not count singles.	Low	High
16. Skate (ice, roller, in-line)?	Low	Low
17. Play a musical instrument?	High	Low
18. Read?	High	Low
19. Do heavy work around the house (such as washing windows, cleaning gutters)?	Low	Low
20. Do light work around the house (such as sweeping or vacuuming)?	Low	Low
21. Do heavy gardening (such as digging, raking)?	Low	Low
22. Do light gardening (such as watering plants)?	Low	Low
23. Work on your car, truck, lawn mower, or other machinery?	Medium	Low
24. Jog or run? Include use of a treadmill.	Low	Low
25. Walk uphill or hike uphill? Count only uphill part. Include use of a treadmill.	Low	Low

	Cognitive Demand Rating	Social Demand Rating
26. Walk fast or briskly for exercise? Do not count walking leisurely or uphill. Include use of a treadmill.	Low	Low
27. Walk to do errands (such as to/from a shop or to take children to school)? Count walk time only.	Low	Low
28. Walk leisurely for exercise or pleasure?	Low	Low
29. Ride a bicycle or stationary cycle?	Low	Low
30. Do other aerobic machines such as rowing, or step machines? Do not count treadmill or stationary cycle.	Low	Low
31. Do water exercise? Do not count other swimming.	Low	Low
32. Swim moderately or fast?	Low	Low
33. Swim gently?	Low	Low
34. Do stretching or flexibility exercises? Do not count yoga or Tai-chi.	Low	Low
35. Do yoga or Tai-chi?	Low	Medium
36. Do aerobics or aerobic dancing?	Low	Medium
37. Do moderate to heavy strength training (such as hand-held weights of more than 5lbs, weight machines, or push-ups)?	Low	Low
38. Do light strength training (such as hand-helf weights of 5 lbs or less or elastic bands)?	Low	Low
39. Do general conditioning exercises, such as light calisthenics or chair exercises? Do not count strength training.	Low	Low
40. Play basketball, football, or squash? Do not count time on sidelines.	Low	High

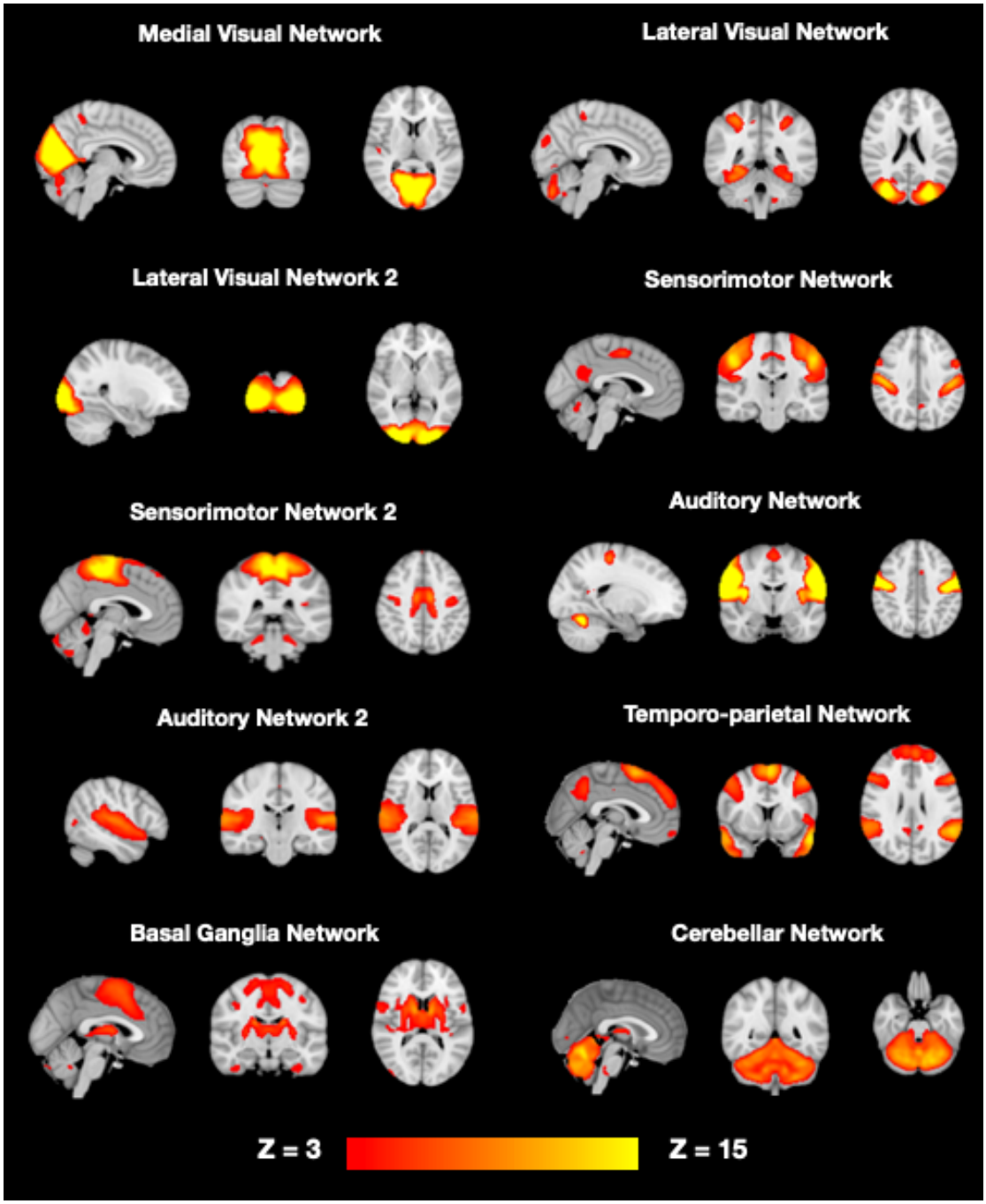
Appendix 3.3 A description of each test within the Whitehall II cognitive battery. For further details, please see Filippini et al. (2014).

Cognitive test	Description
MoCA (Nasreddine et al., 2005)	The MoCA is a 10-minute cognitive screening test that assesses multiple domains, including visuospatial abilities, executive function and language. This test integrates a range of sub-tests, such as the naming of low-familiarity animals, short-term memory recall task, a clock-drawing task, a three-dimension cube copy task, alphanumeric trail making, phonemic fluency task, verbal abstraction task, digit forward and backward and orientation. MoCA scores ranges from 0 – 30, with higher scores reflecting better overall cognition. An additional one point is given to an individual with less than 12 years of education. In a clinical setting, scores below 26 may indicate cognitive impairment (Nasreddine et al., 2005).
Digit span (Wechsler, 2008)	In this task, a trained psychology graduate read out a series of numbers. Participants were either required to recall the numbers in the same order (digit forward), in reverse order (digit backward) or from smallest to largest number (digit sequence). The outcome was the maximum number of digits correctly recalled, under each condition.
Digit Coding (Wechsler, 2008)	Participants were presented with a key that contained a series of numbers, with a unique symbol associated with each number. In a grid containing just numbers, the main task was to draw the correct symbol paired with each number (as stated in the key), within a 2-minute period. The outcome was the total number of correct digit symbol matches.
Language fluency (adapted from ACE-III; Hsieh et al. 2013)	This task required individuals to list as many words as possible starting with the letter 'S' (verbal fluency) or name as many animals as possible (category fluency) within a 60 second time frame. The outcome was the number of words recalled for each type of language fluency.
TMT A and B (Reitan, 1958)	For the trail making tasks, participants were instructed to connect a series of distributed circles on a page consisting of 25 numbers (TMT A) or numbers and letters (TMT B) as quickly and as accurately as possible. The outcome was the time taken to correctly complete the trail (seconds).

RCF (Osterrieth, 1944)	Participants were presented with a complex geometric diagram that they were initially asked to copy. The image was then removed, with individuals immediately instructed to redraw the diagram, this time, from memory (outcome 1: immediate recall score). After a delay, participants were required to once more draw the image from memory (outcome 2: delayed recall score). In the final section of the RCF, participants were presented with several geometric shapes, and asked whether they formed part of the original complex diagram (outcome 3: recognition score).
HVLT-R (Brandt, 1991)	This test required individuals to learn a list of 12 words (drawn from three semantic categories, such as precious gems or vegetables), through three learning trials. A delayed recall task was then administered with a delay of 20-25 minutes, which was followed by subsequent recognition task. For the recognition task, individuals were presented with 24 words and required to identify whether a given word had been in the original list of words to learn (12 were correct). This task therefore provided a measure of delayed recall, recognition and total recall.
CANTAB RTI (CANTABeclipse 5.0; Cambridge Cognition Ltd)	This computerized test (delivered on a touchscreen table) consisted of a simple and choice reaction time task. The simple reaction time task instructed individuals to maintain their finger on a button on the screen until a yellow dot appeared, with the task being to move their finger to the yellow dot as quickly as possible. Under this condition, the yellow dot had only one possible location that it could appear in. In the choice reaction time task, the yellow dot could appear in one of five locations. The outcomes were reaction time (i.e. time to release the button) and movement time (i.e. time taken to touch the yellow dot after releasing the button) in each task.

Abbreviations- ACE-III = Addenbrooke's Cognitive Examination Revised; CANTAB RTI = Cambridge Neuropsychological Test Automated Battery Reaction Time touchscreen task; HVLT-R = Hopkins Verbal Learning Test Revised; RCF = Rey-Osterrieth Complex Figure; RDI = Recognition discrimination index; TMT = Trail making test.

Appendix 3.4 Components representing post-hoc networks.



Appendix 3.5 Table of comparisons between included (n=624) and excluded (n=176) participants.

	Included	**Excluded**	**Test-statistic (d.f.)**	**p-value**
N	624	176		
Age at scan	**69.51± 5**	**71.11 ± 5.63**	**t = 3.397 (257.954)***	**0.001**
MoCA	**27.31 ± 2.19**	**26.6 ± 2.61**	**t = -3.276 (246.942)***	**0.001**
Education	**3.53 ± 1.07**	**3.34 ± 1.08**	**t = -2.059 (797)**	**0.04**
N of females (%)	116 (18.59%)	36 (19.89%)	$\chi2$ = 0.310 (1)	0.578
N of married individuals (%)	**489 (78.4%)**	**116 (65.91%)**	**$\chi2$ = 10.847 (1)**	**< 0.001**
N of retired individuals (%)	516 (82.69%)	154 (87.5%)	$\chi2$ =2.844 (1)	0.092

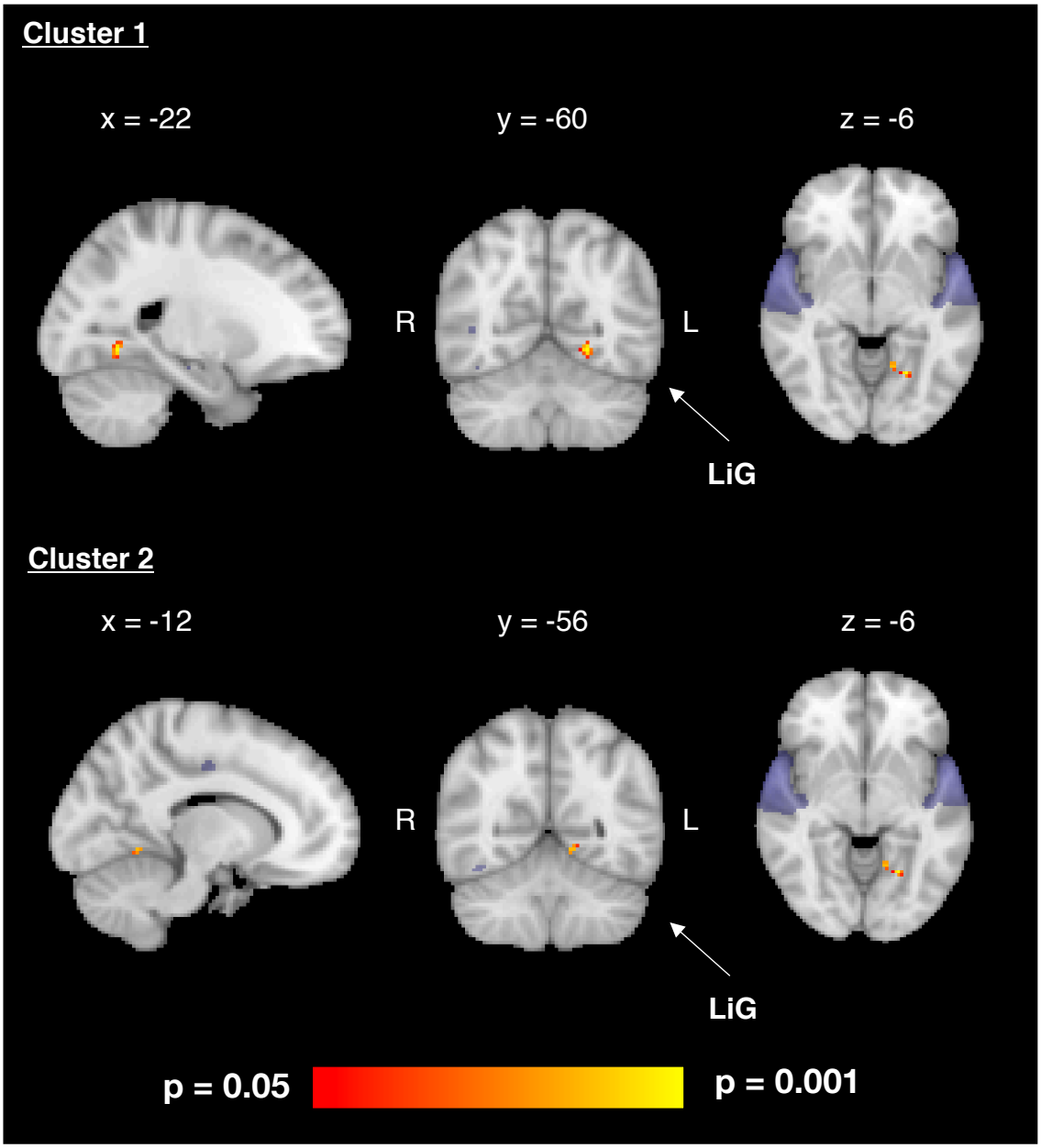
Abbreviations- d.f. = Degrees of Freedom; MoCA = Montreal Cognitive Assessment; N = Number.
Mean±Standard Deviation.
*Levene's test of unequal variances was significant ($p < 0.05$), therefore Welch's t-test was reported.

Appendix 3.6 A table to summarize the results of the post-hoc analyses, evaluating whether leisure activity levels are related to intra-network connectivity of resting-state networks outside of those of interest.

	Model 1 - sociodemographic co-variates				Model 2 - health and lifestyle co-variates			
	B	**SE**	**β**	**p-value**	**B**	**SE**	**β**	**p-value**
Cognitive activities								
Medial VN	-0.011	0.021	-0.02	0.623				
Lateral VN[a]	-0.027	0.015	-0.074	0.066				
Lateral VN 2[a]	-0.001	0.001	-0.055	0.173				
SMN[a]	0.000	0.001	-0.036	0.371				
SMN 2[a]	-0.001	0.001	-0.053	0.182				
AN	0.002	0.013	0.006	0.875				
AN 2[a]	0.000	0.000	0.029	0.462				
TPN	**-0.016**	**0.008**	**-0.078**	**0.046**	**-0.012**	**0.011**	**-0.059**	**0.250**
BGN	-0.005	0.006	-0.035	0.385				
CN[a]	0.000	0.000	-0.009	0.819				
Social activities								
Medial VN	-0.014	0.027	-0.021	0.599				
Lateral VN[a]	-0.021	0.019	-0.046	0.257				
Lateral VN 2[a]	0.000	0.001	-0.006	0.879				
SMN[a]	-0.001	0.001	-0.045	0.255				
SMN 2[a]	-0.001	0.001	-0.072	0.071				
AN	-0.011	0.017	-0.026	0.514				
AN 2[a]	-1.78E-05	0.000	-0.001	0.97				
TPN	-0.019	0.01	-0.073	0.064				
BGN	-0.005	0.008	-0.026	0.507				
CN[a]	0.000	0.001	0.012	0.764				

Abbreviations- AN = Auditory Network; BGN = Basal Ganglia Network; CN = Cerebellar Network; SMN = Sensorimotor Network; TPN = Temporo-parietal Network.
[a]Log-transformed due to skewed variable.
Bold = p <0.05.

Appendix 3.7 Results of voxel-wise post-hoc analyses examining additional resting-state networks. Red-yellow clusters overlaid on a MNI152 standard template demonstrate that functional connectivity between the auditory network and the left lingual gyrus correlated positively with cognitive activity levels, at a $p < 0.05$ (corrected for multiple comparisons across voxels and adjusted for age, sex, educational level, marital status and retirement status and scanner model). Blue clusters indicate the spatial extent of the auditory network.



Appendix 3.8 A summary of post-hoc linear regressions, examining whether social activity levels are related to performance on individual tests.

	Model 1 - sociodemographic co-variates				Model 2 - health and lifestyle co-variates			
	B	**SE**	**β**	**p-value**	**B**	**SE**	**β**	**p-value**
Executive function								
Digit span (forward)	-0.001	0.007	-0.007	0.858				
Digit span (backward)	-0.003	0.007	-0.013	0.733				
Digit span (sequence)	0.008	0.007	0.045	0.254				
Category fluency	0.002	0.016	0.004	0.917				
Letter fluency	0.021	0.014	0.062	0.119				
TMT (B)[a]	-0.001	0.001	-0.066	0.079				
Memory								
HVLT-R (Total recall)	-0.002	0.013	-0.007	0.854				
HVLT-R (Delayed recall)	0.001	0.007	0.005	0.890				
HVLT-R (RDI) skewed -original	0.007	0.006	0.046	0.243				
RCF (Immediate recall)	-0.020	0.019	-0.040	0.296				
RCF (Delayed recall)	-0.015	0.018	-0.032	0.415				
RCF (Recognition)	0.007	0.006	0.046	0.243				
Processing speed								
TMT (A)[a]	-0.001	0.000	-0.082	0.033	-7.426E-05	0.001	-0.007	0.884
Digit coding	0.056	0.038	0.057	0.134				
Simple (Reaction time)[a]	0.000	0.000	-0.067	0.095				
Choice (Reaction time)[a]	-0.195	0.154	-0.050	0.207				
Simple (Movement time)[a]	-0.001	0.000	-0.107	0.007	-0.001	0.000	-0.069	0.175
Choice (Movement time)[a]	-0.495	0.232	-0.085	0.033	-0.475	0.296	-0.081	0.108

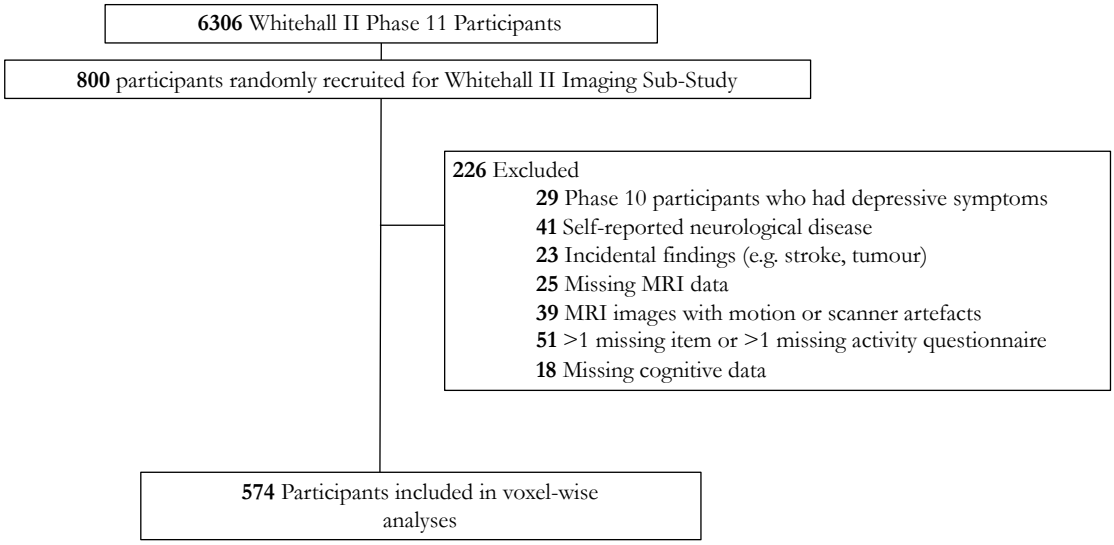
Abbreviations- HVLT-R = Hopkins Verbal Learning Test Revised; RCF = Rey-Osterrieth Complex Figure; RDI = Recognition discrimination index; TMT = Trail making test.

[a]Log-transformed due to skewed variable.

Bold = p<0.05.

Chapter 4 Appendices

Appendix 4.1 Flowchart of participant selection and exclusion.



Abbreviations- WM = White matter.

Appendix 4.2 Cognitive and social demand ratings for each of the items of the WHII activity questionnaire.

	Cognitive Demand Rating	Social Demand Rating
Q1: Religious activities/ observance.	Medium	High
Q2: Positions of office, school governor, councillor ect.	High	High
Q3: Involvement in clubs and organisations, voluntary or official. (Phase 5) *Or* Voluntary work (Phase 7 onwards).	Medium	High
Q4: Courses and educational/ evening classes.	High	Medium
Q5: Cultural visits to stately homes, galleries, theatres, cinema or live music events.	High	Medium
Q6: Social indoor games, cards, bingo, chess, ect.	High	High
Q7: Visiting friends and relatives.	Medium	High
Q8: Going to pubs and social clubs.	Medium	High
Q9: Individual occupations, e.g. reading, listening to music	High	Low
Q10: Household tasks, e.g. DIY, maintenance, decorating.	Low	Low
Q11: Practical activities, making things with your hands, e.g. pottery, drawing, ect.	Medium	Low
Q12: Gardening.	Low	Low
Q13: Using a home computer for leisure.	High	Low

Figure 4.3. Schematic diagram of a quadratic latent growth curve model.
Squares represent indicator variables, which in this case are social activity scores obtained at each of the study phases (i.e. Phases 5 – 11). Note that each of the social activity measures have their own error terms (i.e. σ_e^2). Growth factors are represented by circles, which in this example consist of intercepts (i.e. mean social activity level at the time point coded as "0"), linear slopes and quadratic slopes (change in social activities across time) with variances of these growth factors (i.e. individual differences in intercepts/linear slopes/quadratic slopes) also modelled (i.e. $\sigma_i^2, \sigma_s^2, \sigma_q^2$). Covariances between growth factors are not included in the diagram to help improve the overall clarity of the figure. Based on Figure 4 in King et al. (2017).(King et al., 2017)

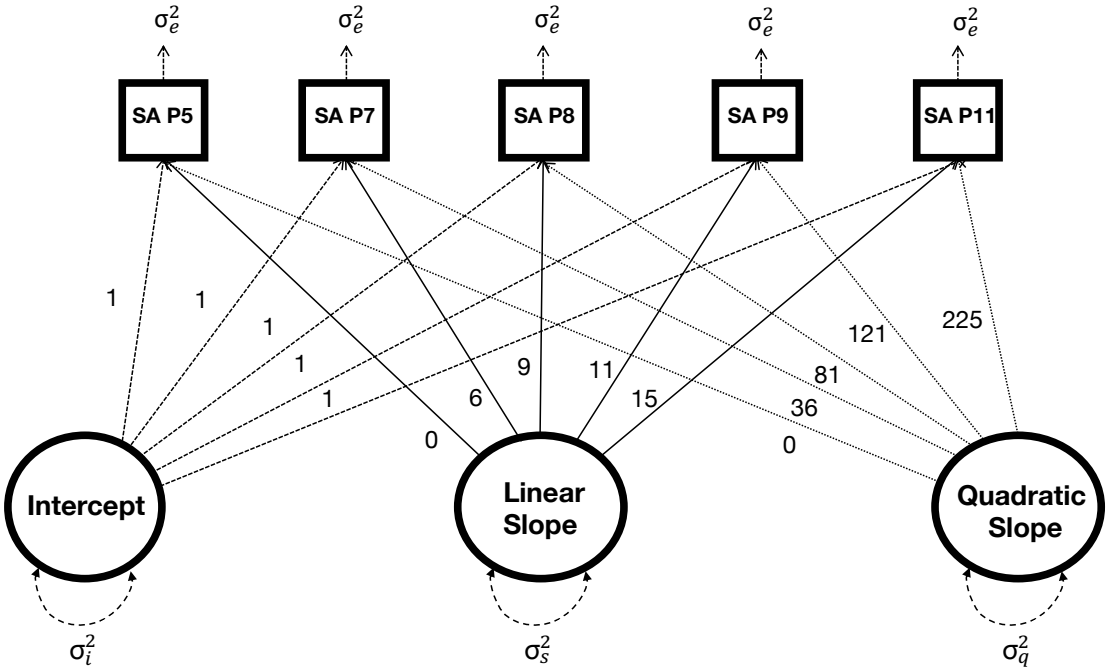
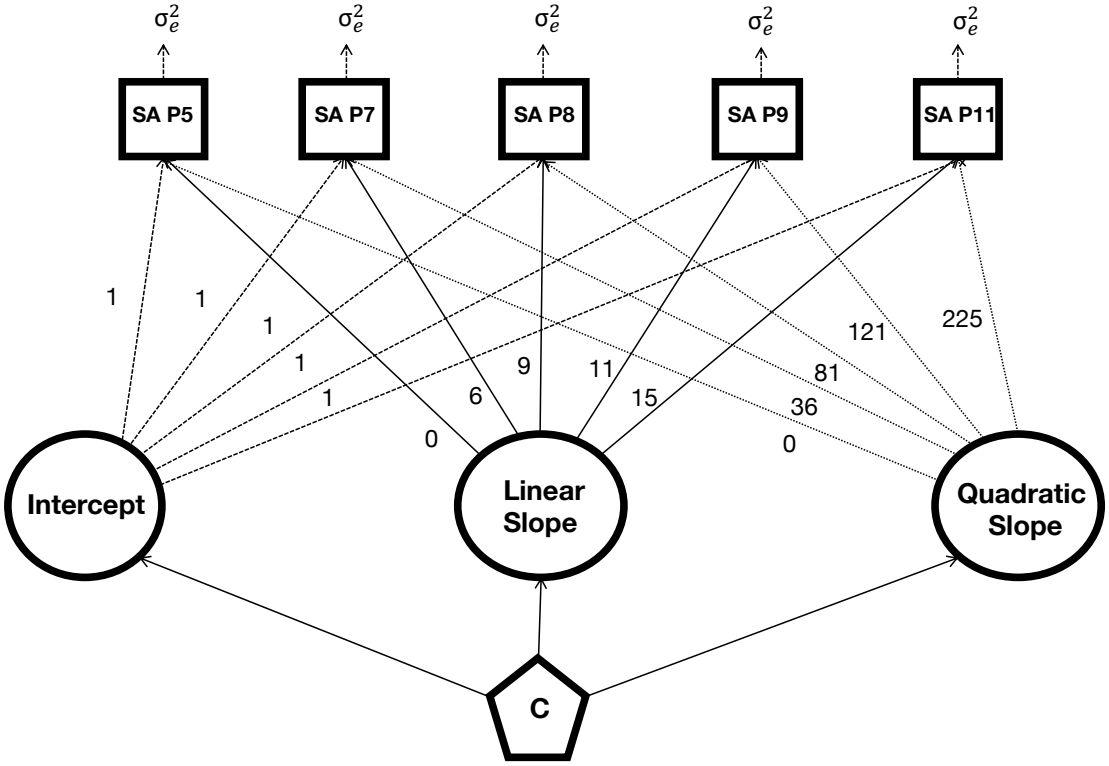


Figure 4.4 Schematic diagram of a quadratic latent class growth model.
Note that the main difference between the latent growth curve model (Figure 1) and the diagram here is the addition of a "C" representing the number of classes extracted (i.e. n, n+1). As one of the core assumption of latent class growth models is that there is no variance *within* the classes extracted, the variance terms associated with the growth factors have also been excluded (i.e. $\sigma_i^2, \sigma_s^2, \sigma_q^2$). Based on Figure 10 in King et al. (2017).(King et al., 2017)

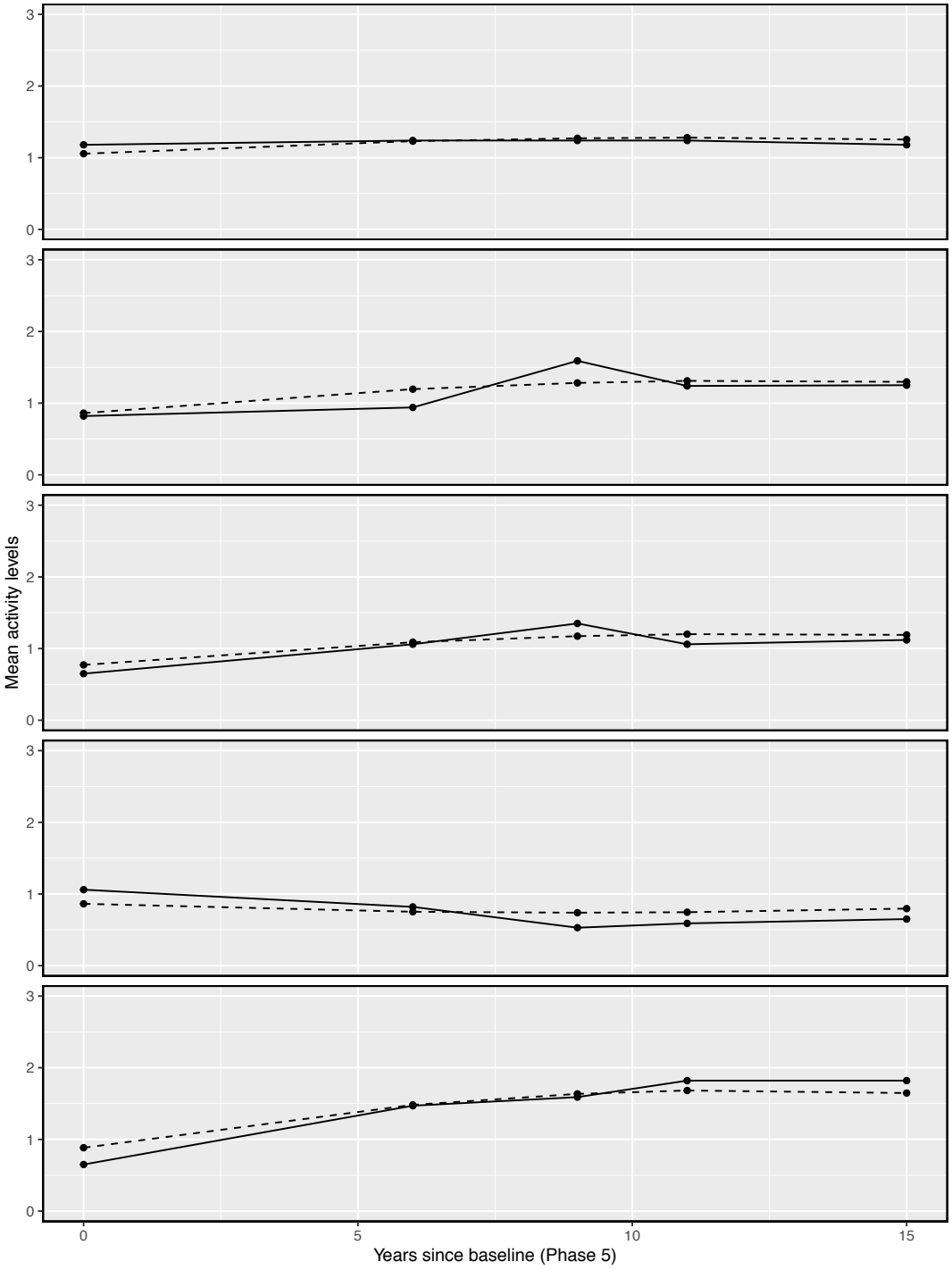


Appendix 4.5 Table describing each of the fit indices used to assess the LCGM and LGCMs.

Index	Abbreviation	Description	Adequate fit	Available for	
				LGCM	LCGM
Akaike Information Criteria (Akaike, 1974)	AIC	Relative fit index that assesses the trade-off between model fit and the number of parameters of the model (i.e. model complexity; Kenny, 2015). The AIC penalizes by two for each additional parameter added.	Lower is better	✓	✓
Bayesian Information Criteria (Schwarz, 1978)	BIC	Relative fit index that penalizes for model complexity, with the penalty increasing as sample size increases (Kenny, 2015).	Lower is better	✓	✓
Sample Size Adjusted BIC (Sclove, 1987)	SSA-BIC	Relative fix index that penalizes to a lesser extent than the BIC, based on sample size (Kenny, 2015).	Lower is better	✓	✓
Tucker-Lewis Index (Tucker and Lewis, 1973)	TLI	Compares the discrepancy in the chi-square of a null model (i.e. where all of the variables are uncorrelated) versus the model of interest. Therefore, a TLI of 0.95 suggests that the model of interest has an 95% improvement in fit relative to a null model (Moss, 2009).	≥ 0.95	✓	×
Comparative Fit Index (Bentler, 1990)	CFI	Evaluates the fit of a given model relative to a null model to assess the discrepancy in fit between the two (Moss, 2009).	≥ 0.95	✓	×
Root Mean Square Error of Approximation (Steiger and Lind, 1980)	RMSEA	Absolute measure of fit, similar to the TLI in that it penalizes for model complexity based on the ratio between the chi-square and degrees of freedom (Kenny, 2015; Moss, 2009).	≥ 0.1	✓	×
Lo-Mendell-Rubin Likelihood Ratio Test (Lo et al., 2001)	LRT-RT	Examines the null hypothesis that a model with one less sub-group (n-1 sub-groups) fits the data equally well (Lo et al., 2001).	$p < 0.05$	×	✓
Bootstrapped LRT (McLachlan and Peel, 2000)	BLRT	This is similar to LMR-LRT method but instead uses bootstrap samples (Nylund et al., 2007).	$p < 0.05$	×	✓
Entropy	N/A	Ranges from 0-1 and serves as an index of the model's confidence in the group classifications (Ram and Grimm, 2009)	≥ 0.8	×	✓

Abbreviations- AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; BLRT = Bootstrap likelihood ratio test; CFI = Comparative fit index; LCGM = Latent class growth model; LGCM = Latent growth curve model; LMR-LRT = Lo-Mendel-Rubin likelihood ratio test; RMSEA = Root Mean Square Error of Approximation; SSA-BIC = Sample size adjusted Bayesian Information Criterion; TLI = Tucker-Lewis Index.

Appendix 4.6 Example of predicted versus actual trajectories of five randomly selected Whitehall II participants. Dashed lines represent predicted trajectories, while solid lines are observed trajectories. The FSCORES method was used to derive predicted trajectories from MPLUS. Specifically, the FSCORES (random effects) method calculates expected trajectories by weighting together (1) each individual's observed values and (2) parameters estimated by the model. In other words, curve estimation for each individual was in part determined by information provided by other participants involved in the study, based on the assumption that everyone was sampled from the same population (L. Muthén 2018, personal communication, 24th September 2018).



Appendix 4.7 Comparisons of included (n = 574) versus excluded (n = 226) participants.

	Included	Excluded	Test-statistic (d.f)	p-value
N.	574	226		
Age at scan	**69.57 ± 4.93**	**70.6 ± 5.72**	**t = 2.370 (363.487)***	**0.018**
MoCA	**27.38 ± 2.11**	**26.56 ± 2.66**	**t = -4.138 (340.711)***	**< 0.001**
Education	**3.54 ± 1.06**	**3.35 ± 1.11**	**t = -2.166 (395.258)**	**0.031**
N of females (%)	106 (18.5%)	46 (20.4%)	$\chi2 = 0.375$ (1)	0.549
N of married individuals (%)	**451 (78.6%)**	**154 (68.14%)**	**$\chi2 = 9.017$ (1)**	**0.003**
N of retired individuals (%)	478 (83.28%)	192 (84.96%)	$\chi2$ 0.506 (1)	0.477

Abbreviations- d.f. = Degrees of Freedom; MoCA = Montreal Cognitive Assessment; N = Number.
Mean ± Standard Deviation.
*Levene's test was significant ($p < 0.05$), therefore Welch's t-test reported.

Appendix 4.8 Regression coefficients for cognitive activities.

Linear regression analyses were used to investigate whether intercepts, linear coefficients and quadratic coefficients of cognitive activities are associated with cognitive function, measures of brain structure and functional connectivity. Model 1 results are adjusted for age, sex and educational level, retirement status and marital status with further adjustments made for scanner model and head motion in the regressions related to MRI outcomes. Model 2 results further adjusted for BMI, BP (MAP), depressive symptoms, sleep quality, units of alcohol and physical activity levels.

		Model 1 – socio-demographic co-variates				**Model 2 – health and lifestyle co-variates**			
Dependent Variable	**Predictors (CA)**	**B**	**SE**	**β**	**p-value**	**B**	**SE**	**β**	**p-value**
Cognitive function									
Global cognition	**Intercept Coefficient**	**0.811**	**0.293**	**0.119**	**0.006**	**0.898**	**0.295**	**0.132**	**0.002**
	Linear Coefficient[a]	-0.321	0.902	-0.014	0.722				
	Linear Coefficient[b]	-0.916	0.945	-0.041	0.332				
	Quadratic Coefficient	**-1.096**	**0.509**	**-0.097**	**0.032**	**-1.237**	**0.512**	**-0.109**	**0.016**
Executive function	**Intercept Coefficient**	**1.633**	**0.514**	**0.132**	**0.002**	**1.745**	**0.512**	**0.141**	**0.001**
	Linear Coefficient[a]	0.648	1.582	0.016	0.682				
	Linear Coefficient[b]	-0.338	1.660	-0.008	0.839				
	Quadratic Coefficient	**-1.811**	**0.894**	**-0.088**	**0.043**	**-2.014**	**0.891**	**-0.097**	**0.024**
Memory	**Intercept Coefficient**	**1.199**	**0.567**	**0.091**	**0.035**	**1.199**	**0.574**	**0.091**	**0.037**
	Linear Coefficient[a]	0.892	1.746	0.021	0.610				
	Linear Coefficient[b]	-0.189	1.824	-0.004	0.918				
	Quadratic Coefficient	**-1.996**	**0.982**	**-0.091**	**0.043**	**-1.994**	**0.994**	**-0.091**	**0.045**
Processing speed	**Intercept Coefficient**	**1.413**	**0.545**	**0.110**	**0.010**	**1.543**	**0.541**	**0.121**	**0.004**
	Linear Coefficient[a]	0.212	1.677	0.005	0.899				
	Linear Coefficient[b]	-0.493	1.758	-0.012	0.779				
	Quadratic Coefficient	-1.292	0.947	-0.061	0.173				
Brain structure									
Global GM volume (% of ICV)	Intercept Coefficient	0.406	0.233	0.065	0.082				
	Linear Coefficient[a]	1.097	0.720	0.054	0.128				
	Linear Coefficient[b]	0.606	0.752	0.030	0.421				
	Quadratic Coefficient	**-0.907**	**0.403**	**-0.087**	**0.025**	**-0.898**	**0.405**	**-0.086**	**0.027**
Global WM volume (% of ICV)	Intercept Coefficient	0.011	0.230	0.001	0.963				
	Linear Coefficient[a]	0.536	0.711	0.022	0.451				
	Linear Coefficient[b]	0.713	0.743	0.029	0.338				

	Quadratic Coefficient	0.324	0.398	0.026	0.416
Global WM lesions (% of ICV)[a]	Intercept Coefficient	-0.031	0.027	-0.046	0.253
	Linear Coefficient[a]	-0.097	0.083	-0.045	0.242
	Linear Coefficient[b]	-0.083	0.087	-0.038	0.340
	Quadratic Coefficient	0.028	0.047	0.025	0.552
Left Hippocampus (% of ICV)[a]	Intercept Coefficient	-0.002	0.005	-0.020	0.626
	Linear Coefficient[a]	0.000	0.015	0.001	0.976
	Linear Coefficient[b]	-8.217E-05	0.016	0.000	0.996
	Quadratic Coefficient	-0.001	0.008	-0.005	0.908
Right Hippocampus (% of ICV)	Intercept Coefficient	-0.007	0.004	-0.069	0.097
	Linear Coefficient[a]	0.001	0.014	0.004	0.927
	Linear Coefficient[b]	0.006	0.014	0.018	0.656
	Quadratic Coefficient	0.009	0.008	0.054	0.216
FA	Intercept Coefficient	0.000	0.002	-0.002	0.954
	Linear Coefficient[a]	0.006	0.007	0.031	0.417
	Linear Coefficient[b]	0.007	0.008	0.036	0.358
	Quadratic Coefficient	0.002	0.004	0.020	0.623
AD ($x10^3$)	Intercept Coefficient	0.003	0.003	0.037	0.361
	Linear Coefficient[a]	-0.001	0.010	-0.004	0.917
	Linear Coefficient[b]	-0.006	0.010	-0.023	0.568
	Quadratic Coefficient	-0.009	0.006	-0.069	0.105
MD ($x10^3$)	Intercept Coefficient	0.002	0.003	0.022	0.580
	Linear Coefficient[a]	-0.006	0.010	-0.022	0.567
	Linear Coefficient[b]	-0.011	0.011	-0.039	0.321
	Quadratic Coefficient	-0.006	0.006	-0.038	0.353
RD ($x10^3$)	Intercept Coefficient	0.001	0.003	0.014	0.719
	Linear Coefficient[a]	-0.008	0.011	-0.028	0.450
	Linear Coefficient[b]	-0.011	0.011	-0.039	0.321
	Quadratic Coefficient	-0.006	0.006	-0.038	0.353
Resting-state functional connectivity*					
Anterior DMN	Intercept Coefficient	0.659	0.768	0.035	0.391
	Linear Coefficient[a]	0.609	2.372	0.010	0.797
	Linear Coefficient[b]	-0.263	2.466	-0.004	0.915
	Quadratic Coefficient	-2.403	1.332	-0.077	0.072
DMN (Precuneus)	Intercept Coefficient	-0.888	0.707	-0.052	0.209
	Linear Coefficient[a]	0.426	2.183	0.008	0.845

	Linear Coefficient[b]	0.969	2.261	0.017	0.668
	Quadratic Coefficient	0.461	1.221	0.016	0.706
Posterior DMN	Intercept Coefficient	-0.364	0.486	-0.032	0.455
	Linear Coefficient[a]	0.796	1.502	0.022	0.597
	Linear Coefficient[b]	0.805	1.571	0.022	0.609
	Quadratic Coefficient	0.020	0.842	0.001	0.981
Left FPN	Intercept Coefficient	-0.340	0.674	-0.021	0.614
	Linear Coefficient[a]	1.434	2.081	0.027	0.491
	Linear Coefficient[b]	1.626	2.176	0.031	0.455
	Quadratic Coefficient	0.355	1.167	0.013	0.761
Right FPN	Intercept Coefficient	-0.365	0.598	-0.026	0.542
	Linear Coefficient[a]	0.912	1.847	0.020	0.622
	Linear Coefficient[b]	1.123	1.931	0.025	0.561
	Quadratic Coefficient	0.391	1.035	0.017	0.706
ECN	Intercept Coefficient	0.023	0.546	0.002	0.966
	Linear Coefficient[a]	-0.540	1.688	-0.012	0.749
	Linear Coefficient[b]	-0.834	1.764	-0.019	0.637
	Quadratic Coefficient	-0.541	0.946	-0.024	0.568

Abbreviations- AD = Axial diffusivity; B = Unstandardized Beta Coefficient; β = Standardized Beta Coefficient; CA = Cognitive activity; CSF = Cerebrospinal fluid; DMN = Default mode network; ECN = Executive control network; FA = Fractional anisotropy; FPN = Frontoparietal network; GM = Grey matter; ICV = Intracranial volume; MD = Mean diffusivity; MoCA = Montreal Cognitive Assessment; MRI = Magnetic resonance imaging; SE = Standard error; RD = Radial diffusivity; WM = White matter; WM = White matter lesions.

* measures are intra-network connectivity.

Linear coefficient[a] = adjusting for intercept coefficients

Linear coefficient[b] = adjusting for quadratic coefficients

Appendix 4.9 Regression coefficients for social activities.

Findings of the linear regression analyses evaluating intercepts, linear coefficients and quadratic coefficients of social activities as predictors of cognitive function and brain integrity. For a description of model co-variates, see Appendix 4.8.

		Model 1 – socio-demographic co-variates				Model 2 –health and lifestyle co-variates			
Dependent Variable	**Predictors (SA)**	**B**	**SE**	**β**	**p-value**	**B**	**SE**	**β**	**p-value**
Cognition									
Global cognition	Intercept coefficient	0.192	0.301	0.037	0.523				
	Linear coefficient	-0.407	0.702	-0.029	0.563				
	Quadratic coefficient	0.588	0.591	0.057	0.321				
Executive function	Intercept coefficient	**1.661**	**0.523**	**0.176**	**0.002**	**1.686**	**0.525**	**0.178**	**0.001**
	Linear coefficient	-1.593	1.222	-0.062	0.193				
	Quadratic coefficient	**2.808**	**1.030**	**0.149**	**0.007**	**2.567**	**1.028**	**0.136**	**0.013**
Memory	Intercept coefficient	-0.262	0.580	-0.026	0.652				
	Linear coefficient	0.031	1.355	0.001	0.981				
	Quadratic coefficient	-0.708	1.142	-0.035	0.536				
Processing speed	Intercept coefficient	0.884	0.556	0.091	0.112				
	Linear coefficient	0.711	1.297	0.027	0.584				
	Quadratic coefficient	1.611	1.093	0.083	0.141				
Brain structure									
Global GM volume (% of ICV)	Intercept coefficient	-0.051	0.238	-0.011	0.831				
	Linear coefficient	0.323	0.558	0.025	0.563				
	Quadratic coefficient	-0.604	0.468	-0.063	0.198				
Global WM volume (% of ICV)	Intercept coefficient	-0.145	0.234	-0.025	0.537				
	Linear coefficient	0.478	0.548	0.031	0.384				
	Quadratic coefficient	0.034	0.461	0.003	0.942				
Global WM lesion volume (% of ICV)[a]	Intercept coefficient	-0.004	0.028	-0.009	0.874				
	Linear coefficient	-0.037	0.064	-0.027	0.564				
	Quadratic coefficient	0.042	0.054	0.041	0.439				
Left Hippocampus (% of ICV)[a]	Intercept coefficient	-0.007	0.005	-0.082	0.140				
	Linear coefficient	-0.004	0.012	-0.017	0.722				
	Quadratic coefficient	-0.014	0.010	-0.078	0.155				
Right Hippocampus (% of ICV)	Intercept coefficient	-0.005	0.004	-0.067	0.227				
	Linear coefficient	-0.008	0.010	-0.037	0.438				
	Quadratic coefficient	0.002	0.009	0.014	0.793				

	Intercept coefficient	0.000	0.002	-0.008	0.886
FA	Linear coefficient	0.001	0.006	0.005	0.905
	Quadratic coefficient	0.002	0.005	0.024	0.642
	Intercept coefficient	0.000	0.003	-0.008	0.889
AD ($x10^3$)	Linear coefficient	-7.077E-05	0.008	0.000	0.993
	Quadratic coefficient	-0.009	0.006	-0.078	0.146
	Intercept coefficient	0.000	0.003	0.002	0.972
MD ($x10^3$)	Linear coefficient	-0.001	0.008	-0.003	0.940
	Quadratic coefficient	-0.007	0.007	-0.054	0.298
	Intercept coefficient	0.000	0.004	0.006	0.911
RD ($x10^3$)	Linear coefficient	-0.001	0.008	-0.005	0.920
	Quadratic coefficient	-0.006	0.007	-0.041	0.427
Resting-state functional connectivity*					
	Intercept coefficient	0.132	0.780	0.009	0.865
Anterior DMN	Linear coefficient	-0.220	1.825	-0.006	0.904
	Quadratic coefficient	-2.299	1.533	-0.081	0.134
	Intercept coefficient	-1.169	0.719	-0.090	0.105
DMN (Precuneus)	Linear coefficient	0.200	1.683	0.006	0.905
	Quadratic coefficient	-0.910	1.414	-0.035	0.520
	Intercept coefficient	-0.642	0.495	-0.075	0.196
Posterior DMN	Linear coefficient	0.684	1.159	0.029	0.555
	Quadratic coefficient	-0.897	0.973	-0.052	0.357
	Intercept coefficient	0.240	0.687	0.019	0.727
Left FPN	Linear coefficient	-0.604	1.607	-0.018	0.707
	Quadratic coefficient	-0.324	1.350	-0.013	0.810
	Intercept coefficient	-0.067	0.609	-0.006	0.913
Right FPN	Linear coefficient	-0.204	1.426	-0.007	0.886
	Quadratic coefficient	-0.697	1.198	-0.033	0.561
	Intercept coefficient	0.173	0.556	0.017	0.756
ECN	Linear coefficient	-1.484	1.300	-0.054	0.254
	Quadratic coefficient	-0.590	1.092	-0.029	0.589

Abbreviations- AD = Axial diffusivity; B = unstandardized beta coefficient; β = standardized beta coefficient; CSF = Cerebrospinal fluid; DMN = Default mode network; ECN = Executive control network; FA = Fractional anisotropy; FPN = Frontoparietal network; GM = Grey matter; ICV = Intracranial volume; MD = Mean diffusivity; MoCA = Montreal Cognitive Assessment; MRI = Magnetic resonance imaging; SA = Social activity; SE = Standard error; RD = Radial diffusivity; WM = White matter.

[a]log-transformed due to skewed data.

* measures are intra-network connectivity.

4.10 Table summarizing the results of post-hoc analyses examining whether cognitive activity trajectories associate with intra-network connectivity of resting-state networks outside of the networks of interest (i.e. ECN, DMN, FPN).

Dependent Variable	Predictor (CA)	Model 1 - sociodemographic co-variates			
		B	SE	β	p-value
Medial VN	Intercept Coefficient	-0.016	0.032	-0.022	0.616
	Linear Coefficient[a]	-0.047	0.098	-0.020	0.629
	Linear Coefficient[b]	-0.045	0.103	-0.019	0.660
	Quadratic Coefficient	0.004	0.055	0.003	0.942
Lateral VN	Intercept Coefficient	-0.233	0.873	-0.012	0.789
	Linear Coefficient[a]	1.779	2.677	0.028	0.507
	Linear Coefficient[b]	1.259	2.802	0.020	0.653
	Quadratic Coefficient	-0.937	1.500	-0.029	0.532
Lateral VN 2	Intercept Coefficient	-0.016	1.448	-0.001	0.991
	Linear Coefficient[a]	-1.969	4.456	-0.019	0.659
	Linear Coefficient[b]	-2.531	4.654	-0.024	0.587
	Quadratic Coefficient	-1.051	2.506	-0.019	0.675
SMN*	Intercept Coefficient	0.009	0.032	0.012	0.783
	Linear Coefficient[a]	-0.014	0.098	-0.006	0.885
	Linear Coefficient[b]	-0.042	0.102	-0.018	0.677
	Quadratic Coefficient	-0.053	0.055	-0.044	0.337
SMN 2*	Intercept Coefficient	-0.015	0.033	-0.021	0.640
	Linear Coefficient[a]	0.019	0.101	0.008	0.854
	Linear Coefficient[b]	0.015	0.105	0.006	0.887
	Quadratic Coefficient	-0.007	0.057	-0.006	0.902
AN	Intercept Coefficient	0.445	0.788	0.025	0.572
	Linear Coefficient[a]	0.454	2.425	0.008	0.851
	Linear Coefficient[b]	-0.094	2.532	-0.002	0.970
	Quadratic Coefficient	-1.016	1.363	-0.034	0.456
AN 2	Intercept Coefficient	0.205	0.883	0.010	0.817
	Linear Coefficient[a]	1.117	2.718	0.017	0.681
	Linear Coefficient[b]	0.393	2.837	0.006	0.890
	Quadratic Coefficient	-1.348	1.528	-0.040	0.378
TPN	Intercept Coefficient	-0.058	0.485	-0.005	0.905
	Linear Coefficient[a]	-0.165	1.493	-0.005	0.912
	Linear Coefficient[b]	-0.463	1.558	-0.013	0.766
	Quadratic Coefficient	-0.558	0.839	-0.030	0.506
BGN	Intercept Coefficient	0.385	0.356	0.048	0.280
	Linear Coefficient[a]	-0.880	1.095	-0.034	0.422
	Linear Coefficient[b]	-1.430	1.142	-0.054	0.211
	Quadratic Coefficient	-1.019	0.615	-0.076	0.098
CN*	Intercept Coefficient	-0.008	0.027	-0.013	0.767
	Linear Coefficient[a]	0.082	0.082	0.042	0.313
	Linear Coefficient[b]	0.077	0.085	0.040	0.368
	Quadratic Coefficient	-0.011	0.046	-0.011	0.817

Abbreviations- AN = Auditory Network; BGN = Basal Ganglia Network; CA = Cognitive Activities; CN = Cerebellar Network; SMN = Sensorimotor Network; TPN = Temporo-parietal Network.
*Log-transformed due to skewed variable.

4.11 Table to provide an overview of the findings from post-hoc analyses, evaluating whether social activity trajectories associate with intra-network connectivity of other resting-state networks.

Dependent Variable	Predictor	Model 1 - sociodemographic co-variates			
		B	SE	β	p-value
Medial VN	Intercept Coefficient	-0.011	0.033	-0.020	0.743
	Linear Coefficient	-0.028	0.076	-0.019	0.713
	Quadratic Coefficient	-0.027	0.064	-0.025	0.670
Lateral VN	Intercept Coefficient	-0.930	0.890	-0.063	0.297
	Linear Coefficient	2.205	2.056	0.055	0.284
	Quadratic Coefficient	-3.023	1.752	-0.102	0.085
Lateral VN 2	Intercept Coefficient	-0.192	1.475	-0.008	0.897
	Linear Coefficient	-1.150	3.446	-0.017	0.739
	Quadratic Coefficient	-0.907	2.904	-0.018	0.755
SMN*	Intercept Coefficient	-0.046	0.032	-0.083	0.158
	Linear Coefficient	0.059	0.075	0.039	0.433
	Quadratic Coefficient	-0.138	0.063	-0.125	0.030
SMN 2*	Intercept Coefficient	-0.041	0.033	-0.073	0.217
	Linear Coefficient	0.032	0.078	0.021	0.679
	Quadratic Coefficient	-0.067	0.065	-0.059	0.309
AN	Intercept Coefficient	-0.810	0.802	-0.059	0.313
	Linear Coefficient	0.867	1.874	0.023	0.644
	Quadratic Coefficient	-1.711	1.579	-0.063	0.279
AN 2	Intercept Coefficient	-1.009	0.899	-0.066	0.262
	Linear Coefficient	0.597	2.099	0.014	0.776
	Quadratic Coefficient	-2.256	1.768	-0.074	0.203
TPN	Intercept Coefficient	-0.440	0.493	-0.052	0.373
	Linear Coefficient	-0.542	1.152	-0.023	0.638
	Quadratic Coefficient	-0.982	0.971	-0.058	0.312
BGN	Intercept Coefficient	0.021	0.362	0.003	0.955
	Linear Coefficient	-1.053	0.845	-0.063	0.213
	Quadratic Coefficient	-0.567	0.712	-0.046	0.427
CN*	Intercept Coefficient	-0.030	0.027	-0.065	0.274
	Linear Coefficient	0.104	0.063	0.084	0.100
	Quadratic Coefficient	-0.046	0.053	-0.051	0.382

Abbreviations- AN = Auditory Network; BGN = Basal Ganglia Network; CN = Cerebellar Network; SA = Social Activities; SMN = Sensorimotor Network; TPN = Temporo-parietal Network.
*Log-transformed due to skewed variable.

Table 4.12 Coordinates of the clusters of resting-state functional connectivity associated with cognitive activities. The coordinates are presented in MNI space with the Harvard-Oxford Structural Cortical and Subcortical Atlases (FSLeyes tool) used to identify the brain regions associated with the significant clusters. The direction of all of the described associations were negative and all were significant at a $p < 0.05$ (adjusted for multiple comparisons across voxels and co-variates including age, sex, educational level, retirement status, marital status and scanner model).

Predictor (CA)	Resting-state network	Cluster No.	N of voxels	p-value	MNI coordinates of max voxel			Region
					x	y	z	
Quadratic coefficient	Medial VN	1	9	0.029	-22	-40	2	L Hippocampus
Quadratic coefficient	Medial VN	2	4	0.048	-32	-8	-24	L Hippocampus
Quadratic coefficient	BGN	1	1	0.049	-32	-16	48	L Middle Frontal gyrus

Abbreviations- BGN= Basal Ganglia network; CA = Cognitive activities; L = Left; VN = Visual network.

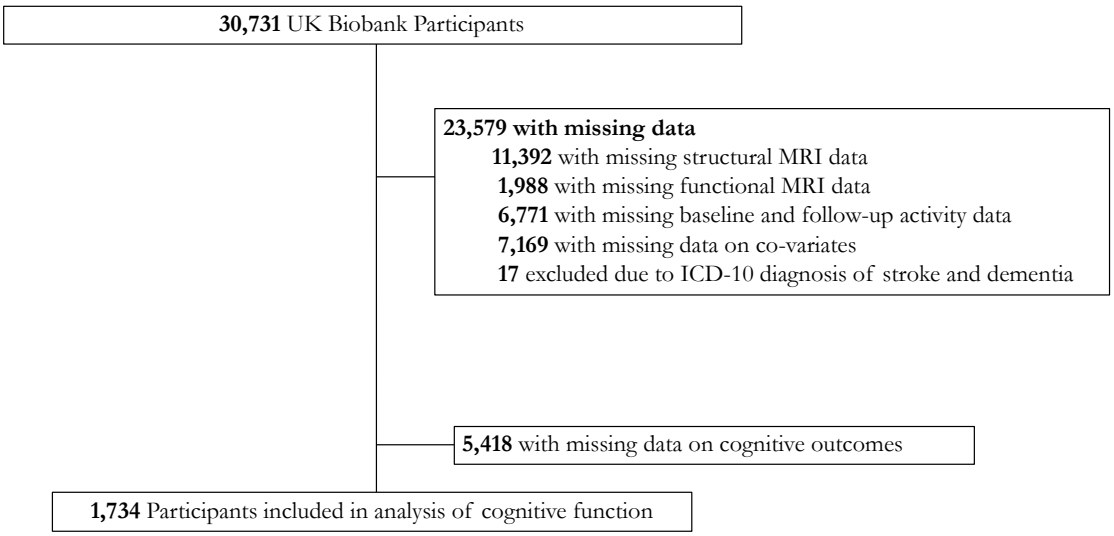
Table 4.13 Coordinates of the clusters of resting-state functional connectivity relating with social activities. The coordinates are presented in MNI space and the Harvard-Oxford Structural Atlas (FSLeyes tool) was used to examined brain regions associated with the significant clusters. The direction of all of the reported associations were negative, with the models adjusted for multiple comparisons across voxels and co-variates including age, sex, educational level, retirement status, marital status and scanner model. An association with a p-value of < 0.05 was considered statistically significant.

Predictor (SA)	Resting-state network	Cluster No.	N of voxels	p-value	MNI coordinates of max voxel			Region
					x	y	z	
Quadratic coefficient	**SMN**	**1**	**123**	**0.014**	**38**	**-32**	**64**	**R Postcentral gyrus**
Quadratic coefficient	**SMN**	**2**	**42**	**0.028**	**52**	**-20**	**58**	**R Postcentral gyrus**
Linear coefficient	TPN	1	7	0.026	26	-72	8	R Intracalcarine cortex
Intercept coefficient	Anterior DMN	1	5	0.034	16	-84	-12	R Occipital Fusiform gyrus
Intercept coefficient	SMN	1	1	0.047	-34	-60	4	L Occipital Fusiform gyrus

Abbreviations- BGN= Basal Ganglia network; L = Left; DMN = Default mode network; R = Right; SA = Social activities; SMN = Sensorimotor network; TPN = Temporo-parietal network.

Chapter 5 Appendices

Appendix 5.1 Flowchart of participant selection and exclusion.



Appendix 5.2 List of regional measures of grey matter (GM) volume.

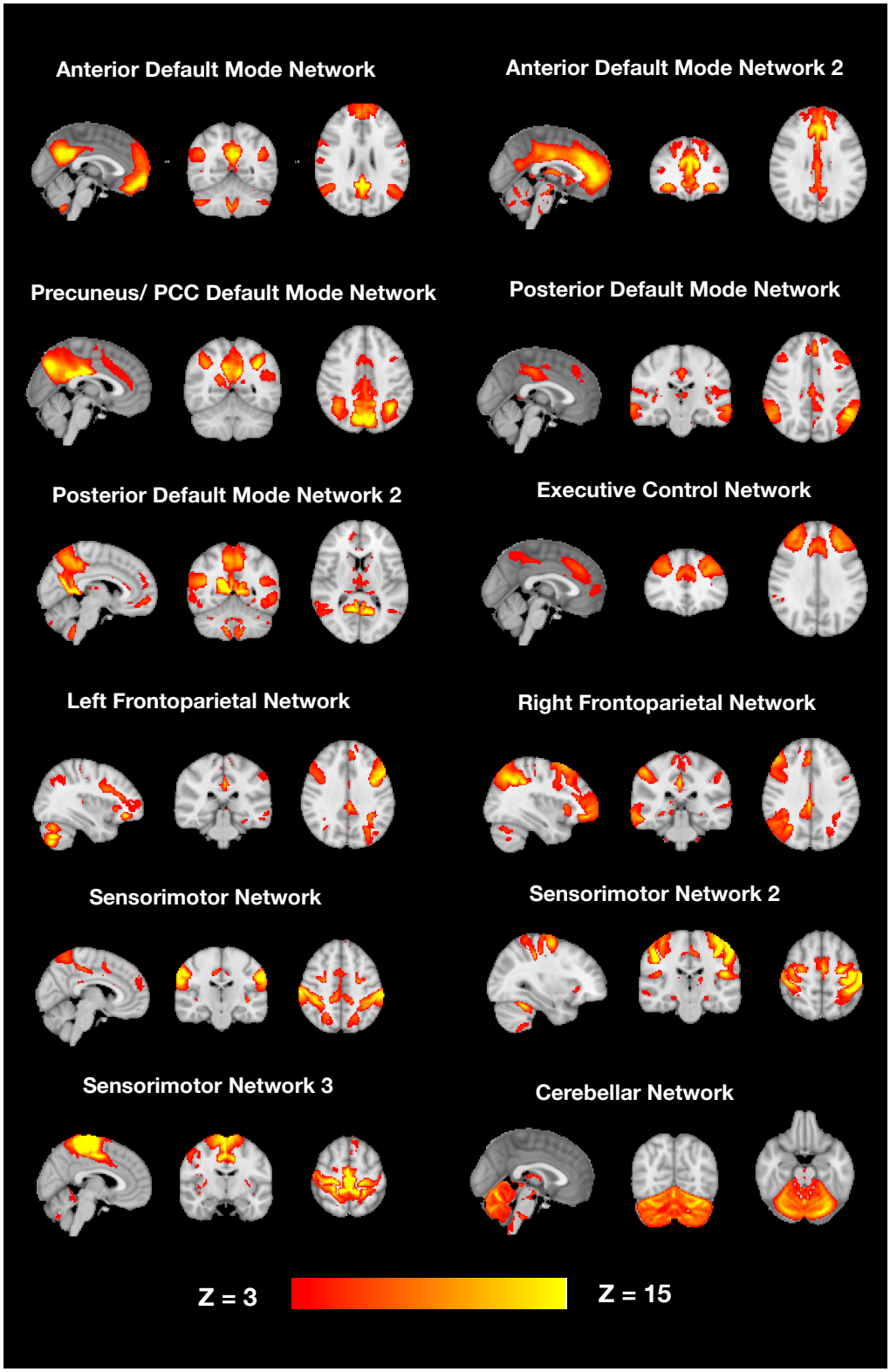
1. volume of accumbens (left)
2. volume of accumbens (right)
3. volume of amygdala (left)
4. volume of amygdala (right)
5. volume of caudate (left)
6. volume of caudate (right)
7. volume of GM in angular gyrus (left)
8. volume of GM in angular gyrus (right)
9. volume of GM in brainstem
10. volume of GM in central opercular cortex (left)
11. volume of GM in central opercular cortex (right)
12. volume of GM in cingulate gyrus anterior division (left)
13. volume of GM in cingulate gyrus anterior division (right)
14. volume of GM in cingulate gyrus posterior division (left)
15. volume of GM in cingulate gyrus posterior division (right)
16. volume of GM in crus i cerebellum (left)
17. volume of GM in crus i cerebellum (right)
18. volume of GM in crus ii cerebellum (left)
19. volume of GM in crus ii cerebellum (right)
20. volume of GM in cuneal cortex (left)
21. volume of GM in cuneal cortex (right)
22. volume of GM in frontal medial cortex (left)
23. volume of GM in frontal medial cortex (right)
24. volume of GM in frontal operculum cortex (left)
25. volume of GM in frontal operculum cortex (right)
26. volume of GM in frontal orbital cortex (left)
27. volume of GM in frontal orbital cortex (right)
28. volume of GM in frontal pole (left)
29. volume of GM in frontal pole (right)
30. volume of GM in heschls gyrus includes h1 and h2 (left)
31. volume of GM in heschls gyrus includes h1 and h2 (right)
32. volume of GM in iiv cerebellum (left)
33. volume of GM in iiv cerebellum (right)
34. volume of GM in inferior frontal gyrus pars opercularis (left)
35. volume of GM in inferior frontal gyrus pars opercularis (right)
72. volume of GM in parahippocampal gyrus anterior division (left)
73. volume of GM in parahippocampal gyrus anterior division (right)
74. volume of GM in parahippocampal gyrus posterior division (left)
75. volume of GM in parahippocampal gyrus posterior division (right)
76. volume of GM in parietal operculum cortex (left)
77. volume of GM in parietal operculum cortex (right)
78. volume of GM in planum polare (left)
79. volume of GM in planum polare (right)
80. volume of GM in planum temporale (left)
81. volume of GM in planum temporale (right)
82. volume of GM in postcentral gyrus (left)
83. volume of GM in postcentral gyrus (right)
84. volume of GM in precentral gyrus (left)
85. volume of GM in precentral gyrus (right)
86. volume of GM in precuneous cortex (left)
87. volume of GM in precuneous cortex (right)
88. volume of GM in subcallosal cortex (left)
89. volume of GM in subcallosal cortex (right)
90. volume of GM in superior frontal gyrus (left)
91. volume of GM in superior frontal gyrus (right)
92. volume of GM in superior parietal lobule (left)
93. volume of GM in superior parietal lobule (right)
94. volume of GM in superior temporal gyrus anterior division (left)
95. volume of GM in superior temporal gyrus anterior division (right)
96. volume of GM in superior temporal gyrus posterior division (left)
97. volume of GM in superior temporal gyrus posterior division (right)
98. volume of GM in supracalcarine cortex (left)
99. volume of GM in supracalcarine cortex (right)
100. volume of GM in supramarginal gyrus anterior division (left)
101. volume of GM in supramarginal gyrus anterior division (right)
102. volume of GM in supramarginal gyrus posterior division (left)
103. volume of GM in supramarginal gyrus posterior division (right)
104. volume of GM in temporal fusiform cortex anterior division (left)
105. volume of GM in temporal fusiform cortex anterior division (right)
106. volume of GM in temporal fusiform cortex posterior division (left)

36. volume of GM in inferior frontal gyrus pars triangularis (left)
37. volume of GM in inferior frontal gyrus pars triangularis (right)
38. volume of GM in inferior temporal gyrus anterior division (left)
39. volume of GM in inferior temporal gyrus anterior division (right)
40. volume of GM in inferior temporal gyrus posterior division (left)
41. volume of GM in inferior temporal gyrus posterior division (right)
42. volume of GM in inferior temporal gyrus temporooccipital part (left)
43. volume of GM in inferior temporal gyrus temporooccipital part (right)
44. volume of GM in insular cortex (left)
45. volume of GM in insular cortex (right)
46. volume of GM in intracalcarine cortex (left)
47. volume of GM in intracalcarine cortex (right)
48. volume of GM in ix cerebellum (left)
49. volume of GM in ix cerebellum (right)
50. volume of GM in juxtapositional lobule cortex formerly supplementary motor cortex (left)
51. volume of GM in juxtapositional lobule cortex formerly supplementary motor cortex (right)
52. volume of GM in lateral occipital cortex inferior division (left)
53. volume of GM in lateral occipital cortex inferior division (right)
54. volume of GM in lateral occipital cortex superior division (left)
55. volume of GM in lateral occipital cortex superior division (right)
56. volume of GM in lingual gyrus (left)
57. volume of GM in lingual gyrus (right)
58. volume of GM in middle frontal gyrus (left)
59. volume of GM in middle frontal gyrus (right)
60. volume of GM in middle temporal gyrus anterior division (left)
61. volume of GM in middle temporal gyrus anterior division (right)
62. volume of GM in middle temporal gyrus posterior division (left)
63. volume of GM in middle temporal gyrus posterior division (right)
64. volume of GM in middle temporal gyrus temporooccipital part (left)
65. volume of GM in middle temporal gyrus temporooccipital part (right)
66. volume of GM in occipital fusiform gyrus (left)
67. volume of GM in occipital fusiform gyrus (right)
68. volume of GM in occipital pole (left)
69. volume of GM in occipital pole (right)
70. volume of GM in paracingulate gyrus (left)
71. volume of GM in paracingulate gyrus (right)
107. volume of GM in temporal fusiform cortex posterior division (right)
108. volume of GM in temporal occipital fusiform cortex (left)
109. volume of GM in temporal occipital fusiform cortex (right)
110. volume of GM in temporal pole (left)
111. volume of GM in temporal pole (right)
112. volume of GM in v cerebellum (left)
113. volume of GM in v cerebellum (right)
114. volume of GM in ventral striatum (left)
115. volume of GM in ventral striatum (right)
116. volume of GM in vermis crus i cerebellum
117. volume of GM in vermis crus ii cerebellum
118. volume of GM in vermis ix cerebellum
119. volume of GM in vermis vi cerebellum
120. volume of GM in vermis viib cerebellum
121. volume of GM in vermis viiia cerebellum
122. volume of GM in vermis viiib cerebellum
123. volume of GM in vermis x cerebellum
124. volume of GM in vi cerebellum (left)
125. volume of GM in vi cerebellum (right)
126. volume of GM in viib cerebellum (left)
127. volume of GM in viib cerebellum (right)
128. volume of GM in viiia cerebellum (left)
129. volume of GM in viiia cerebellum (right)
130. volume of GM in viiib cerebellum (left)
131. volume of GM in viiib cerebellum (right)
132. volume of GM in x cerebellum (left)
133. volume of GM in x cerebellum (right)
134. volume of hippocampus (left)
135. volume of hippocampus (right)
136. volume of pallidum (left)
137. volume of pallidum (right)
138. volume of putamen (left)
139. volume of putamen (right)
140. volume of thalamus (left)
141. volume of thalamus (right)

Appendix 5.3 List of white matter tracts.

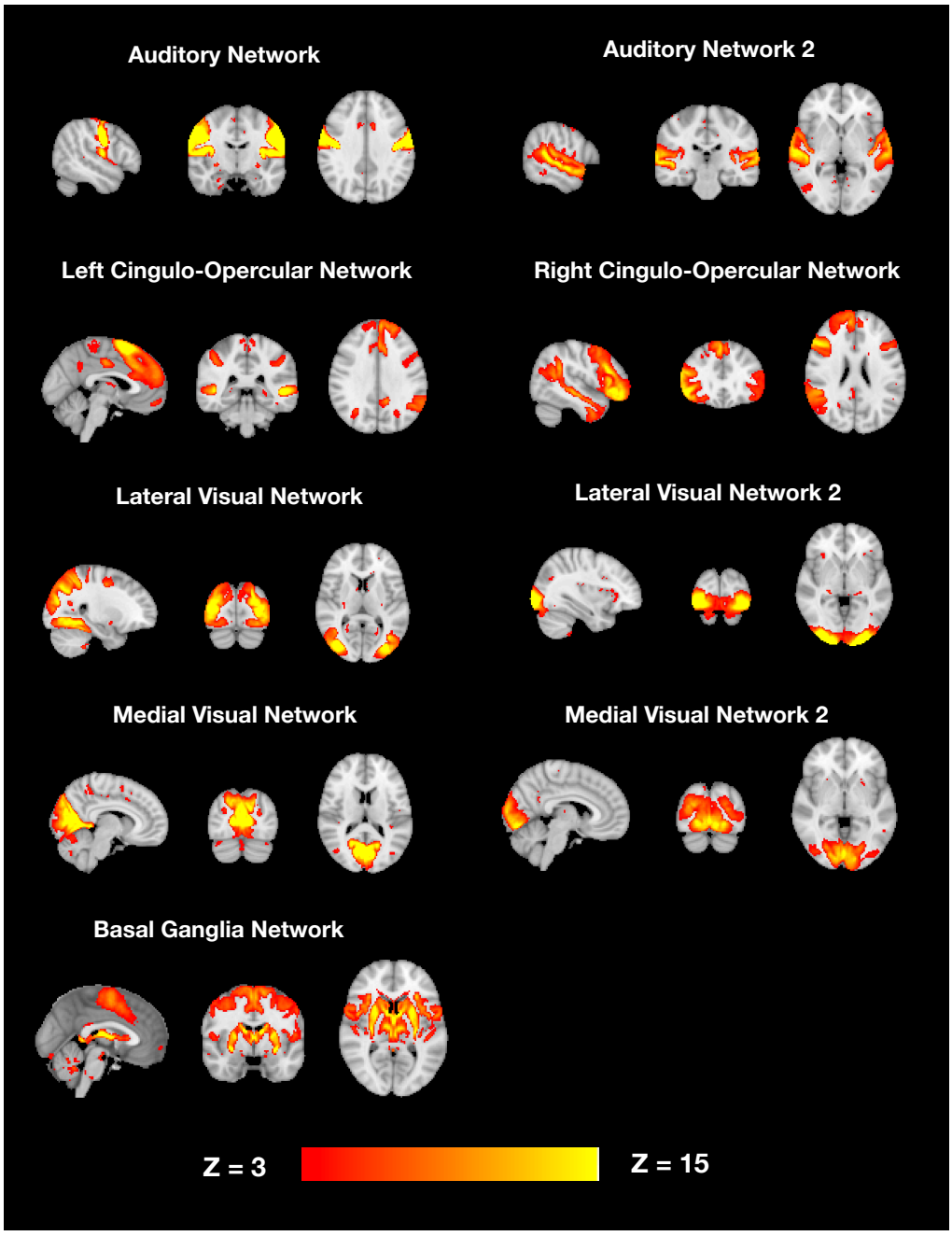
1. anterior thalamic radiation (right)
2. anterior thalamic radiation (left)
3. forceps minor
4. inferior frontooccipital fasciculus (right)
5. inferior frontooccipital fasciculus (left)
6. uncinate fasciculus (right)
7. superior thalamic radiation (left)
8. superior longitudinal fasciculus (left)
9. superior thalamic radiation (right)
10. inferior longitudinal fasciculus (right)
11. cingulate gyrus part of cingulum (left)
12. corticospinal tract (left)
13. inferior longitudinal fasciculus (left)
14. posterior thalamic radiation (left)
15. uncinate fasciculus (left)
16. corticospinal tract (right)
17. superior longitudinal fasciculus (right)
18. medial lemniscus (right)
19. acoustic radiation (right)
20. forceps major
21. posterior thalamic radiation (right)
22. parahippocampal part of cingulum (right)
23. cingulate gyrus part of cingulum (right)
24. middle cerebellar peduncle
25. acoustic radiation (left)
26. parahippocampal part of cingulum (left)
27. medial lemniscus (left)

Appendix 5.4 Classifications of signal components from a 25-dimension ICA.



Abbreviations – PCC = Posterior Cingulate Cortex.

Appendix 5.4 *continued.* Classifications of signal components derived from a 25-dimension ICA.



Appendix 5.5 Table of comparisons between included and excluded individuals.

Dependent variable	Included	Excluded	Test-statistic	p-value	FDR q-value
Age at baseline (years)	54.571	56.385	t = -18.286	< 0.001	< 0.001
Sex (% female)	4897 (54.48%)	4897 (51.05%)	$\chi 2$ = 25.925	< 0.001	< 0.001
Educational level	4.071	4.174	t = -6.914	< 0.001	< 0.001
Occupational status	4.702	6.105	t = -29.068	< 0.001	< 0.001
Alcohol (frequency/ week)	3.257	3.414	t = -8.541	< 0.001	< 0.001
BMI (kg/m^2)	26.821	26.4	t = 7.577	< 0.001	< 0.001
N. in household	2.556	2.442	t = 7.433	< 0.001	< 0.001
Sleep duration (hours/ night)	7.148	7.215	t = -5.284	< 0.001	< 0.001
Head motion	0.123	0.119	t = 4.965	< 0.001	< 0.001
% of individuals with ICD-10 diagnosis of depression/ anxiety	51 (0.71%)	181 (0.78%)	$\chi 2$ = 0.218	0.641	0.76
BP (MAP)	99.512	99.575	t = -0.39	0.697	0.76
Head size	1.299	1.299	t = 0.144	0.886	0.89

Abbreviations- BMI = Body mass index; BP = Blood pressure; ICD = International Classification of Diseases; MAP = Mean arterial pressure; N = number.
Note: Due to unequal variances detected between included and excluded participants on continuous variables, Welch's t-test was performed and is reported.

Appendix 5.6 Table of associations between weekly mid-life participation in activities and cognitive function. Results are adjusted for sociodemographic, health and lifestyle co-variates (i.e. Model 3).

Dependent variable	Predictor	B	SE	B	p-value	FDR q-value
Numeric Trail making (sec, log)	**Mid-life computer use**	**-0.040**	**0.009**	**-0.105**	**> 0.001**	**> 0.001**
Alphanumeric trail making (sec, log)	**Mid-life computer use**	**-0.032**	**0.010**	**-0.068**	**0.002**	**0.036**
Fluid intelligence score	Mid-life attendance to social clubs or pubs	-0.226	0.102	-0.056	0.027	0.299
Simple reaction time (sec)	Mid-life participation in sports clubs or gyms	-0.010	0.005	-0.049	0.037	0.299
Fluid intelligence score	Mid-life computer use	0.288	0.146	0.046	0.049	0.299
		OR	**95% C.I.**		**p-value**	**FDR q-value**
Prospective memory score	**Mid-life computer use**	**2.009**	**1.336 - 22.971**		**0.001**	**0.014**

Abbreviations- C.I. = Confidence intervals; OR = Odds ratio.
Bold = survived FDR corrections.

Appendix 5.7 Table of associations between weekly late-life participation in activities and cognitive function. We report the results after adjustments for sociodemographic, health and lifestyle co-variates (i.e. Model 3).

Dependent variable	Predictor	B	SE	B	p-value	FDR q-value
Fluid intelligence score	**Late-life computer use**	**0.701**	**0.200**	**0.082**	**> 0.001**	**0.011**
Alphanumeric trail making (sec, log)	**Late-life computer use**	**-0.049**	**0.014**	**-0.075**	**0.001**	**0.011**
Numeric Trail making (sec, log)	**Late-life computer use**	**-0.039**	**0.012**	**-0.073**	**0.001**	**0.015**
Fluid intelligence score	**Late-life attendance to adult educational classes**	**0.463**	**0.146**	**0.075**	**0.002**	**0.015**
Fluid intelligence score	Late-life attendance to a social club or pub	-0.259	0.102	-0.064	0.011	0.087
Alphanumeric trail making (sec, log)	Late-life attendance to adult educational classes	-0.025	0.010	-0.052	0.019	0.128
Fluid intelligence score	Late-life family and friend visits	-0.246	0.116	-0.049	0.034	0.205
Backward digit span	Late-life computer use	0.268	0.130	0.049	0.039	0.206
		OR	**95% C.I.**		**p-value**	**FDR q-value**
Prospective memory score	**Late-life computer use**	**2.554**	**1.507 - 4.208**		**> 0.001**	**0.011**

Abbreviations- C.I. = Confidence intervals; OR = Odds ratio.
Bold = survived FDR corrections.

Appendix 5.8 Table of associations between weekly mid-life participation in activities and volumetric brain measures. Results are adjusted for sociodemographic, health and lifestyle co-variates (i.e. Model 3).

Dependent Variable	Predictor	B	SE	β	p-value	FDR q-value
volume of putamen (left)	**Mid-life computer use**	**77.429**	**17.534**	**0.042**	**< 0.001**	**0.012**
volume of GM in occipital pole (left)	Mid-life family and friend visits	141.553	36.052	0.040	< 0.001	0.053
volume of putamen (right)	Mid-life computer use	61.071	16.999	0.033	< 0.001	0.143
volume of GM in v cerebellum (right)	Mid-life family and friend visits	-34.862	10.026	-0.037	0.001	0.143
volume of GM in paracingulate gyrus (right)	Mid-life family and friend visits	71.750	21.099	0.034	0.001	0.150
volume of GM in vermis viib cerebellum	Mid-life attendance to social clubs or pubs	-2.400	0.728	-0.041	0.001	0.172
volume of GM in precuneous cortex (right)	Mid-life participation in religious activities	-109.239	33.578	-0.031	0.001	0.172
volume of accumbens (left)	Mid-life computer use	13.055	4.097	0.034	0.001	0.184
volume of putamen (left)	Mid-life participation in religious activities	-42.560	13.709	-0.031	0.002	0.197
volume of GM in crus ii cerebellum (right)	Mid-life participation in religious activities	-95.910	31.111	-0.035	0.002	0.197
volume of GM in occipital pole (right)	Mid-life family and friend visits	104.911	34.452	0.031	0.002	0.211
volume of GM in iiv cerebellum (right)	Mid-life family and friend visits	-25.174	8.437	-0.033	0.003	0.225
volume of hippocampus (left)	Mid-life computer use	48.577	16.395	0.032	0.003	0.233
volume of GM in ventral striatum (right)	Mid-life computer use	10.629	3.662	0.030	0.004	0.254
volume of GM in inferior frontal gyrus pars triangularis (right)	Mid-life computer use	50.651	17.764	0.032	0.004	0.281
volume of GM in temporal pole (left)	Mid-life computer use	109.799	39.281	0.028	0.005	0.305
volume of GM in occipital fusiform gyrus (right)	Mid-life participation in religious activities	-42.894	15.546	-0.031	0.006	0.313
volume of GM in middle temporal gyrus anterior division (left)	Mid-life computer use	35.017	12.991	0.029	0.007	0.313
volume of GM in temporal fusiform cortex anterior division (left)	Mid-life computer use	21.712	8.084	0.028	0.007	0.313
volume of GM in ventral striatum (left)	Mid-life computer use	9.827	3.662	0.027	0.007	0.313
volume of caudate (right)	Mid-life attendance to adult educational classes	35.554	13.473	0.027	0.008	0.339
volume of GM in brainstem	Mid-life attendance to adult educational classes	-72.939	27.954	-0.028	0.009	0.343
volume of GM in temporal pole (right)	Mid-life computer use	99.217	38.061	0.026	0.009	0.343
volume of GM in v cerebellum (left)	Mid-life family and friend visits	-26.550	10.207	-0.028	0.009	0.343
volume of GM in temporal fusiform cortex anterior division (right)	Mid-life computer use	19.237	7.408	0.027	0.009	0.343
volume of GM in vermis viiia cerebellum	Mid-life participation in religious activities	-12.242	4.730	-0.031	0.010	0.343
volume of GM in superior temporal gyrus anterior division (left)	Mid-life computer use	25.851	10.024	0.028	0.010	0.343
volume of GM in vermis vi cerebellum	Mid-life attendance to social clubs or pubs	-15.576	6.050	-0.032	0.010	0.343
volume of GM in vermis crus ii cerebellum	Mid-life participation in sports clubs or gyms	-4.633	1.804	-0.031	0.010	0.343
volume of GM in brainstem	Mid-life attendance to social clubs or pubs	-53.706	20.983	-0.030	0.011	0.343
volume of GM in central opercular cortex (left)	Mid-life attendance to adult educational classes	42.683	16.729	0.025	0.011	0.343
volume of GM in parahippocampal gyrus anterior division (left)	Mid-life computer use	34.155	13.489	0.025	0.011	0.343
volume of GM in supramarginal gyrus anterior division (left)	Mid-life family and friend visits	45.519	17.984	0.028	0.011	0.343
volume of GM in lateral occipital cortex superior division (left)	Mid-life family and friend visits	141.385	55.987	0.025	0.012	0.343

volume of GM in crus ii cerebellum (right)	Mid-life attendance to social clubs or pubs	-72.719	28.820	-0.030	0.012	0.343
volume of GM in iiv cerebellum (left)	Mid-life family and friend visits	-19.658	7.812	-0.028	0.012	0.345
volume of GM in crus ii cerebellum (left)	Mid-life participation in religious activities	-78.007	31.731	-0.028	0.014	0.372
volume of GM in insular cortex (left)	Mid-life computer use	45.262	18.420	0.021	0.014	0.372
volume of GM in insular cortex (right)	Mid-life participation in religious activities	-34.842	14.322	-0.022	0.015	0.375
volume of caudate (right)	Mid-life participation in sports clubs or gyms	21.795	9.032	0.025	0.016	0.381
volume of GM in temporal fusiform cortex anterior division (left)	Mid-life participation in religious activities	15.245	6.321	0.026	0.016	0.381
volume of GM in vermis crus ii cerebellum	Mid-life attendance to social clubs or pubs	-4.836	2.020	-0.031	0.017	0.392
volume of putamen (right)	Mid-life participation in religious activities	-31.768	13.291	-0.023	0.017	0.392
volume of GM in middle temporal gyrus anterior division (right)	Mid-life computer use	25.226	10.614	0.026	0.017	0.392
volume of GM in vermis crus i cerebellum	Mid-life computer use	0.136	0.058	0.028	0.020	0.409
volume of GM in superior temporal gyrus anterior division (right)	Mid-life attendance to adult educational classes	22.651	9.806	0.025	0.021	0.409
volume of GM	Mid-life attendance to social clubs or pubs	-1675.634	725.392	-0.015	0.021	0.409
volume of caudate (left)	Mid-life attendance to social clubs or pubs	21.876	9.478	0.025	0.021	0.409
volume of GM in insular cortex (right)	Mid-life computer use	42.193	18.318	0.020	0.021	0.409
volume of caudate (left)	Mid-life attendance to adult educational classes	29.073	12.628	0.023	0.021	0.409
volume of GM in vermis viiia cerebellum	Mid-life attendance to social clubs or pubs	-9.976	4.382	-0.028	0.023	0.421
volume of GM in vi cerebellum (right)	Mid-life family and friend visits	-60.922	26.766	-0.023	0.023	0.421
volume of GM in precentral gyrus (right)	Mid-life attendance to adult educational classes	117.008	51.424	0.023	0.023	0.421
volume of GM in angular gyrus (right)	Mid-life participation in sports clubs or gyms	-56.025	24.736	-0.025	0.024	0.427
volume of GM in postcentral gyrus (right)	Mid-life family and friend visits	84.104	37.437	0.023	0.025	0.427
volume of GM in vermis viib cerebellum	Mid-life participation in religious activities	-1.755	0.786	-0.027	0.026	0.427
volume of GM in frontal operculum cortex (left)	Mid-life family and friend visits	15.245	6.848	0.024	0.026	0.427
volume of GM in ventral striatum (right)	Mid-life participation in sports clubs or gyms	5.273	2.369	0.023	0.026	0.427
volume of GM in parahippocampal gyrus anterior division (right)	Mid-life attendance to adult educational classes	30.516	13.733	0.022	0.026	0.427
volume of amygdala (left)	Mid-life participation in sports clubs or gyms	12.444	5.607	0.025	0.026	0.427
volume of GM in inferior temporal gyrus temporooccipital part (right)	Mid-life participation in religious activities	-43.080	19.445	-0.024	0.027	0.427
volume of GM in postcentral gyrus (left)	Mid-life family and friend visits	84.362	38.109	0.023	0.027	0.427
volume of GM in planum polare (right)	Mid-life attendance to adult educational classes	14.431	6.525	0.022	0.027	0.427
volume of GM in x cerebellum (left)	Mid-life computer use	5.976	2.704	0.024	0.027	0.427
volume of accumbens (right)	Mid-life computer use	8.250	3.745	0.024	0.028	0.427
volume of GM in frontal pole (left)	Mid-life family and friend visits	126.062	57.371	0.018	0.028	0.428
volume of GM in lingual gyrus (right)	Mid-life attendance to adult educational classes	54.488	25.123	0.020	0.030	0.443
volume of GM in vermis crus i cerebellum	Mid-life participation in religious activities	-0.097	0.046	-0.027	0.033	0.461
volume of hippocampus (left)	Mid-life participation in religious activities	-27.208	12.819	-0.024	0.034	0.461
volume of GM in cingulate gyrus anterior division (left)	Mid-life attendance to adult educational classes	72.624	34.527	0.023	0.035	0.461
volume of GM in middle temporal gyrus anterior division (left)	Mid-life participation in religious activities	21.342	10.157	0.023	0.036	0.461
volume of GM in crus i cerebellum (right)	Mid-life attendance to social clubs or pubs	-87.569	41.697	-0.024	0.036	0.461
volume of GM in temporal fusiform cortex posterior division (left)	Mid-life computer use	36.005	17.147	0.020	0.036	0.461

volume of GM in vermis viiia cerebellum	Mid-life family and friend visits	-10.050	4.815	-0.023	0.037	0.469
volume of GM in middle temporal gyrus anterior division (left)	Mid-life participation in sports clubs or gyms	17.511	8.403	0.023	0.037	0.469
volume of GM	Mid-life attendance to adult educational classes	2009.258	966.394	0.012	0.038	0.469
volume of GM in superior temporal gyrus posterior division (left)	Mid-life attendance to adult educational classes	32.485	15.800	0.022	0.040	0.469
volume of GM in superior temporal gyrus anterior division (left)	Mid-life participation in religious activities	16.098	7.838	0.023	0.040	0.469
volume of GM in viiia cerebellum (left)	Mid-life attendance to social clubs or pubs	-34.926	17.023	-0.024	0.040	0.469
volume of GM in inferior temporal gyrus temporooccipital part (left)	Mid-life participation in sports clubs or gyms	-27.559	13.434	-0.023	0.040	0.469
volume of GM in frontal orbital cortex (right)	Mid-life participation in sports clubs or gyms	29.574	14.421	0.020	0.040	0.469
volume of GM in crus i cerebellum (right)	Mid-life participation in religious activities	-92.171	45.012	-0.023	0.041	0.469
volume of GM in vi cerebellum (left)	Mid-life family and friend visits	-56.654	27.728	-0.021	0.041	0.469
volume of GM	Mid-life participation in religious activities	-1596.327	783.057	-0.013	0.042	0.469
volume of GM in parahippocampal gyrus posterior division (right)	Mid-life attendance to adult educational classes	11.883	5.842	0.022	0.042	0.469
volume of hippocampus (right)	Mid-life computer use	33.537	16.521	0.022	0.042	0.469
volume of GM in paracingulate gyrus (left)	Mid-life family and friend visits	41.866	20.634	0.020	0.042	0.469
volume of GM in x cerebellum (right)	Mid-life computer use	5.414	2.670	0.022	0.043	0.469
volume of thalamus (right)	Mid-life participation in religious activities	-29.767	14.700	-0.018	0.043	0.469
volume of GM in inferior frontal gyrus pars triangularis (left)	Mid-life family and friend visits	33.177	16.535	0.023	0.045	0.472
volume of GM in frontal operculum cortex (left)	Mid-life participation in sports clubs or gyms	11.017	5.566	0.022	0.048	0.484
volume of GM in crus ii cerebellum (left)	Mid-life attendance to social clubs or pubs	-57.983	29.394	-0.024	0.049	0.485
volume of GM in central opercular cortex (right)	Mid-life attendance to adult educational classes	34.439	17.497	0.019	0.049	0.487
volume of GM in inferior temporal gyrus anterior division (left)	Mid-life computer use	21.060	10.715	0.022	0.049	0.488
volume of white matter	Mid-life participation in religious activities	-1768.355	903.981	-0.012	0.050	0.493

Abbreviations- GM = Grey matter.
Bold = survived FDR corrections.

Appendix 5.9 Table of associations between weekly late-life participation in activities and volumetric brain measures. The reported associations are adjusted for sociodemographic, imaging, health and lifestyle co-variates (i.e. Model 3).

Dependent Variable	Predictor	B	SE	β	p-value	FDR q-value
volume of hippocampus (left)	Late-life computer use	80.416	23.304	0.038	0.001	0.256
volume of putamen (left)	Late-life participation in religious activities	-45.291	13.557	-0.033	0.001	0.256
volume of thalamus (left)	Late-life participation in sports clubs or gyms	39.043	12.873	0.026	0.002	0.345
volume of putamen (right)	Late-life participation in religious activities	-39.007	13.138	-0.029	0.003	0.345
volume of GM in precuneous cortex (left)	Late-life computer use	-165.336	56.679	-0.027	0.004	0.345
volume of GM in lateral occipital cortex inferior division (right)	Late-life attendance to adult educational classes	124.161	43.191	0.029	0.004	0.345
volume of GM in occipital pole (left)	Late-life family and friend visits	103.865	37.253	0.029	0.005	0.345
volume of GM in temporal fusiform cortex posterior division (left)	Late-life computer use	67.507	24.363	0.027	0.006	0.345
volume of GM in inferior temporal gyrus posterior division (right)	Late-life attendance to adult educational classes	-70.249	25.450	-0.029	0.006	0.345
volume of GM in insular cortex (left)	Late-life computer use	72.265	26.189	0.024	0.006	0.345
volume of hippocampus (right)	Late-life computer use	64.636	23.482	0.030	0.006	0.345
volume of GM in precuneous cortex (right)	Late-life participation in religious activities	-89.811	33.178	-0.026	0.007	0.357
volume of GM in precentral gyrus (left)	Late-life computer use	203.124	75.920	0.026	0.007	0.357
volume of pallidum (right)	Late-life attendance to social clubs or pubs	-15.734	5.884	-0.031	0.008	0.357
volume of GM in inferior frontal gyrus pars opercularis (left)	Late-life attendance to social clubs or pubs	-34.813	13.400	-0.031	0.009	0.357
volume of GM in v cerebellum (right)	Late-life computer use	46.162	17.918	0.027	0.010	0.363
volume of caudate (left)	Late-life computer use	47.645	18.615	0.025	0.011	0.363
volume of GM in planum polare (right)	Late-life participation in sports clubs or gyms	-11.151	4.373	-0.025	0.011	0.363
volume of GM in occipital pole (right)	Late-life family and friend visits	89.521	35.600	0.025	0.012	0.369
volume of white matter	Late-life family and friend visits	2365.984	950.375	0.015	0.013	0.377
volume of thalamus (right)	Late-life participation in sports clubs or gyms	29.946	12.149	0.021	0.014	0.399
volume of GM in inferior temporal gyrus temporooccipital part (right)	Late-life attendance to adult educational classes	62.069	25.609	0.025	0.015	0.437
volume of GM in frontal operculum cortex (left)	Late-life computer use	29.463	12.236	0.026	0.016	0.447
volume of GM in inferior temporal gyrus temporooccipital part (right)	Late-life attendance to social clubs or pubs	42.792	17.776	0.027	0.016	0.447
volume of GM in occipital fusiform gyrus (right)	Late-life participation in religious activities	-36.687	15.361	-0.027	0.017	0.460
volume of GM in x cerebellum (right)	Late-life computer use	8.889	3.796	0.025	0.019	0.499
volume of GM in frontal operculum cortex (right)	Late-life computer use	27.169	11.646	0.025	0.020	0.506
volume of GM in vermis crus i cerebellum	Late-life family and friend visits	0.111	0.048	0.028	0.020	0.510
volume of GM in insular cortex (right)	Late-life computer use	60.129	26.041	0.020	0.021	0.517
volume of GM in middle temporal gyrus anterior division (left)	Late-life participation in religious activities	22.847	10.040	0.025	0.023	0.542
volume of GM in vi cerebellum (right)	Late-life computer use	107.390	47.821	0.023	0.025	0.550
volume of GM in vermis viib cerebellum	Late-life attendance to social clubs or pubs	-1.616	0.720	-0.028	0.025	0.550
volume of GM in frontal operculum cortex (right)	Late-life participation in sports clubs or gyms	11.821	5.297	0.025	0.026	0.562
volume of GM in ventral striatum (right)	Late-life attendance to social clubs or pubs	-5.789	2.621	-0.024	0.027	0.564

volume of GM in frontal pole (left)	Late-life attendance to adult educational classes	-160.275	74.311	-0.018	0.031	0.602
volume of GM in v cerebellum (left)	Late-life computer use	38.963	18.235	0.023	0.033	0.613
volume of GM in planum polare (left)	Late-life participation in sports clubs or gyms	-9.258	4.349	-0.022	0.033	0.621
volume of GM in iiv cerebellum (right)	Late-life computer use	31.983	15.075	0.023	0.034	0.623
volume of GM in temporal fusiform cortex anterior division (right)	Late-life participation in sports clubs or gyms	-10.052	4.792	-0.022	0.036	0.624
volume of GM in planum temporale (right)	Late-life participation in sports clubs or gyms	-13.541	6.456	-0.021	0.036	0.624
volume of GM in vermis vi cerebellum	Late-life computer use	24.546	11.876	0.023	0.039	0.652
volume of GM in superior temporal gyrus posterior division (right)	Late-life family and friend visits	29.600	14.344	0.021	0.039	0.652
volume of GM in insular cortex (right)	Late-life participation in sports clubs or gyms	24.434	11.844	0.018	0.039	0.652
volume of GM in inferior temporal gyrus temporooccipital part (right)	Late-life participation in religious activities	-39.561	19.195	-0.023	0.039	0.652
volume of GM in ventral striatum (left)	Late-life attendance to social clubs or pubs	-5.364	2.621	-0.022	0.041	0.665
volume of GM in postcentral gyrus (right)	Late-life family and friend visits	79.061	38.679	0.021	0.041	0.665
volume of GM in temporal pole (left)	Late-life computer use	114.102	55.857	0.020	0.041	0.665
volume of GM in vi cerebellum (left)	Late-life computer use	100.957	49.542	0.021	0.042	0.666
volume of GM in juxtapositional lobule cortex formerly supplementary motor cortex (left)	Late-life attendance to social clubs or pubs	27.425	13.776	0.023	0.047	0.701
volume of GM in x cerebellum (left)	Late-life attendance to adult educational classes	-5.502	2.788	-0.021	0.048	0.701
volume of GM in vermis crus i cerebellum	Late-life attendance to social clubs or pubs	-0.082	0.042	-0.025	0.049	0.701

Abbreviations- GM = Grey matter.
Bold = survived FDR corrections.

Appendix 5.10 Table to show associations between weekly mid-life participation in activities and tract-averaged FA and MD. Results are adjusted for sociodemographic, imaging, health and lifestyle co-variates (i.e. Model 3).

Dependent Variable	Predictor	B	SE	β	p-value	FDR q-value
FA in anterior thalamic radiation (right)	Mid-life computer use	-0.002	0.001	-0.036	0.002	0.197
FA in anterior thalamic radiation (left)	Mid-life computer use	-0.002	0.001	-0.034	0.002	0.217
FA in cingulate gyrus part of cingulum (left)	Mid-life computer use	-0.004	0.001	-0.034	0.004	0.254
FA in superior thalamic radiation (left)	Mid-life computer use	-0.002	0.001	-0.034	0.004	0.264
FA in corticospinal (left)	Mid-life computer use	-0.002	0.001	-0.029	0.013	0.360
FA in superior thalamic radiation (right)	Mid-life computer use	-0.002	0.001	-0.028	0.015	0.375
MD in superior longitudinal fasciculus (right)	Mid-life participation in sports clubs or gyms	0.000	0.000	0.028	0.015	0.375
FA in superior longitudinal fasciculus (left)	Mid-life computer use	-0.002	0.001	-0.027	0.018	0.395
FA in acoustic radiation (left)	Mid-life computer use	-0.002	0.001	-0.028	0.019	0.399
MD in middle cerebellar peduncle	Mid-life computer use	0.000	0.000	-0.027	0.019	0.404
MD in parahippocampal part of cingulum (right)	Mid-life family and friend visits	0.000	0.000	-0.026	0.025	0.427
MD in acoustic radiation (right)	Mid-life computer use	0.000	0.000	0.026	0.027	0.427
MD in cingulate gyrus part of cingulum (right)	Mid-life attendance to adult educational classes	0.000	0.000	0.025	0.032	0.458
MD in forceps minor	Mid-life participation in religious activities	0.000	0.000	-0.025	0.042	0.469
FA in anterior thalamic radiation (right)	Mid-life attendance to adult educational classes	-0.001	0.001	-0.023	0.043	0.469
FA in cingulate gyrus part of cingulum (right)	Mid-life family and friend visits	0.002	0.001	0.023	0.046	0.475
MD in uncinate fasciculus (left)	Mid-life attendance to social clubs or pubs	0.000	0.000	0.025	0.047	0.481
MD in forceps major	Mid-life attendance to adult educational classes	0.000	0.000	-0.024	0.050	0.492

Abbreviations- FA = Fractional Anisotropy; MD = Medial Diffusivity.
Bold = survived FDR corrections.

Appendix 5.11 A table to demonstrate associations between weekly late-life participation in activities and tract-averaged FA and MD. These associations are adjusted for sociodemographic, imaging, health and lifestyle co-variates (i.e. Model 3).

Dependent Variable	Predictor	B	SE	β	p-value	FDR q-value
FA in anterior thalamic radiation (left)	Late-life attendance to adult educational classes	-0.002	0.001	-0.034	0.003	0.345
FA in anterior thalamic radiation (right)	Late-life attendance to adult educational classes	-0.002	0.001	-0.034	0.003	0.345
MD in cingulate gyrus part of cingulum (right)	Late-life attendance to adult educational classes	0.000	0.000	0.033	0.005	0.345
MD in superior longitudinal fasciculus (left)	Late-life attendance to adult educational classes	0.000	0.000	0.030	0.008	0.357
MD in inferior frontooccipital fasciculus (right)	Late-life attendance to adult educational classes	0.000	0.000	0.030	0.008	0.357
MD in superior longitudinal fasciculus (right)	Late-life attendance to adult educational classes	0.000	0.000	0.030	0.009	0.357
MD in cingulate gyrus part of cingulum (left)	Late-life attendance to adult educational classes	0.000	0.000	0.031	0.009	0.357
FA in forceps minor	Late-life attendance to adult educational classes	-0.002	0.001	-0.030	0.009	0.357
MD in anterior thalamic radiation (left)	Late-life attendance to adult educational classes	0.000	0.000	0.027	0.010	0.362
MD in anterior thalamic radiation (right)	Late-life attendance to adult educational classes	0.000	0.000	0.027	0.011	0.363
MD in middle cerebellar peduncle	Late-life computer use	0.000	0.000	-0.029	0.011	0.365
MD in inferior frontooccipital fasciculus (left)	Late-life attendance to adult educational classes	0.000	0.000	0.027	0.018	0.467
FA in middle cerebellar peduncle	Late-life participation in religious activities	-0.002	0.001	-0.028	0.022	0.535
FA in inferior frontooccipital fasciculus (right)	Late-life attendance to adult educational classes	-0.002	0.001	-0.027	0.022	0.535
FA in inferior frontooccipital fasciculus (left)	Late-life attendance to adult educational classes	-0.002	0.001	-0.026	0.024	0.542
MD in inferior longitudinal fasciculus (right)	Late-life attendance to adult educational classes	0.000	0.000	0.025	0.026	0.562
MD in middle cerebellar peduncle	Late-life participation in sports clubs or gyms	0.000	0.000	-0.026	0.026	0.562
MD in uncinate fasciculus (left)	Late-life participation in religious activities	0.000	0.000	-0.026	0.028	0.568
FA in acoustic radiation (right)	Late-life computer use	-0.002	0.001	-0.025	0.032	0.602
FA in anterior thalamic radiation (left)	Late-life family and friend visits	0.001	0.001	0.024	0.032	0.610
FA in superior thalamic radiation (left)	Late-life computer use	-0.002	0.001	-0.024	0.036	0.624
MD in acoustic radiation (left)	Late-life attendance to social clubs or pubs	0.000	0.000	0.026	0.044	0.674
MD in forceps minor	Late-life attendance to adult educational classes	0.000	0.000	0.024	0.044	0.674

Abbreviations- FA = Fractional Anisotropy; MD = Medial Diffusivity.
Bold = survived FDR corrections.

Appendix 5.12 Table to show the associations between weekly mid-life participation in activities and resting-state functional connectivity. Results are adjusted for sociodemographic, imaging, health and lifestyle co-variates (i.e. Model 3).

Dependent Variable	Predictor	B	SE	β	p-value	FDR q-value
Connectivity between SMN 3 and Lateral VN 2	**Mid-life participation in sports clubs or gyms**	**0.063**	**0.014**	**0.056**	**0.000**	**0.009**
Connectivity between SMN 3 and CN	**Mid-life participation in sports clubs or gyms**	**0.062**	**0.014**	**0.051**	**0.000**	**0.015**
Connectivity between SMN and Posterior DMN	Mid-life attendance to social clubs or pubs	0.085	0.024	0.046	0.000	0.143
Connectivity between L FPN and AN	Mid-life family and friend visits	0.055	0.016	0.041	0.001	0.143
Connectivity between AN and CN	Mid-life participation in sports clubs or gyms	0.045	0.013	0.042	0.001	0.143
Connectivity between Medial VN and R CON	Mid-life attendance to social clubs or pubs	0.049	0.014	0.045	0.001	0.143
Connectivity between SMN 3 and BN	Mid-life participation in sports clubs or gyms	-0.052	0.015	-0.040	0.001	0.169
Connectivity between Posterior DMN and SMN 3	Mid-life participation in sports clubs or gyms	0.043	0.013	0.040	0.001	0.170
Connectivity between SMN 2 and Lateral VN 2	Mid-life computer use	0.084	0.026	0.039	0.001	0.172
Connectivity between R FPN and BN	Mid-life family and friend visits	-0.056	0.017	-0.038	0.001	0.172
Connectivity between SMN 3 and Precuneus/PCC DMN	Mid-life participation in sports clubs or gyms	0.043	0.013	0.039	0.001	0.184
Connectivity between Medial VN and Lateral VN 2	Mid-life attendance to social clubs or pubs	0.114	0.036	0.041	0.002	0.184
Connectivity between SMN 2 and SMN 3	Mid-life attendance to adult educational classes	0.110	0.036	0.037	0.002	0.197
Connectivity between L FPN and SMN 2	Mid-life participation in sports clubs or gyms	0.057	0.018	0.038	0.002	0.197
Connectivity between AN and SMN 3	Mid-life participation in sports clubs or gyms	0.053	0.017	0.037	0.002	0.197
Connectivity between Medial VN and ECN	Mid-life attendance to adult educational classes	0.071	0.024	0.036	0.003	0.217
Connectivity between R FPN and Anterior DMN 2	Mid-life participation in sports clubs or gyms	-0.054	0.018	-0.037	0.003	0.218
Connectivity between SMN 2 and SMN 3	Mid-life participation in sports clubs or gyms	0.069	0.024	0.035	0.004	0.254
Connectivity between ECN and AN 2	Mid-life participation in sports clubs or gyms	-0.059	0.020	-0.035	0.004	0.254
Connectivity between Medial VN 2 and SMN 2	Mid-life participation in sports clubs or gyms	0.055	0.019	0.034	0.005	0.305
Connectivity between ECN and Lateral VN 2	Mid-life participation in sports clubs or gyms	0.050	0.018	0.034	0.005	0.305
Connectivity between SMN and Medial VN 2	Mid-life attendance to adult educational classes	-0.085	0.030	-0.034	0.005	0.305
Connectivity between Anterior DMN and Lateral VN 2	Mid-life family and friend visits	0.057	0.020	0.033	0.005	0.308
Connectivity between CN and Precuneus/PCC DMN	Mid-life family and friend visits	-0.044	0.016	-0.032	0.006	0.311
Connectivity between AN and AN 2	Mid-life computer use	0.068	0.025	0.033	0.006	0.313
Connectivity between SMN 3 and Anterior DMN 2	Mid-life computer use	-0.050	0.018	-0.033	0.006	0.313
Connectivity between SMN 2 and CN	Mid-life participation in sports clubs or gyms	0.048	0.018	0.033	0.007	0.313
Connectivity between Anterior DMN 2 and R CON	Mid-life family and friend visits	-0.056	0.021	-0.032	0.007	0.313
Connectivity between Lateral VN and SMN 2	Mid-life participation in religious activities	-0.069	0.025	-0.034	0.007	0.313
Connectivity between SMN 3 and Lateral VN 2	Mid-life participation in religious activities	0.044	0.016	0.034	0.007	0.313
Connectivity between Anterior DMN and Precuneus/PCC DMN	Mid-life participation in sports clubs or gyms	0.057	0.021	0.032	0.007	0.313
Connectivity between AN and BN	Mid-life family and friend visits	-0.052	0.019	-0.032	0.007	0.313
Connectivity between CN and AN 2	Mid-life participation in sports clubs or gyms	0.040	0.015	0.032	0.007	0.313
Connectivity between R FPN and R CON	Mid-life participation in religious activities	0.074	0.028	0.034	0.007	0.313
Connectivity between SMN 2 and AN	Mid-life participation in religious activities	0.066	0.025	0.033	0.008	0.313

Connectivity between Anterior DMN and R FPN	Mid-life participation in religious activities	0.074	0.028	0.033	0.009	0.343
Connectivity between Anterior DMN and R CON	Mid-life participation in sports clubs or gyms	-0.052	0.020	-0.032	0.009	0.343
Connectivity between Precuneus/PCC DMN and R CON	Mid-life participation in sports clubs or gyms	-0.048	0.019	-0.032	0.010	0.343
Connectivity between Posterior DMN and ECN	Mid-life attendance to social clubs or pubs	-0.062	0.024	-0.034	0.010	0.343
Connectivity between R FPN and SMN 2	Mid-life attendance to adult educational classes	0.066	0.026	0.031	0.011	0.343
Connectivity between Lateral VN and Posterior DMN	Mid-life attendance to adult educational classes	-0.080	0.032	-0.030	0.011	0.343
Connectivity between L FPN and ECN	Mid-life family and friend visits	-0.073	0.029	-0.030	0.011	0.343
Connectivity between Posterior DMN and Lateral VN 2	Mid-life computer use	0.063	0.025	0.030	0.012	0.343
Connectivity between SMN and SMN 3	Mid-life participation in sports clubs or gyms	-0.043	0.017	-0.030	0.012	0.343
Connectivity between Posterior DMN 2 and Lateral VN 2	Mid-life participation in sports clubs or gyms	-0.044	0.017	-0.031	0.012	0.345
Connectivity between L CON and Anterior DMN 2	Mid-life participation in sports clubs or gyms	0.040	0.016	0.031	0.012	0.351
Connectivity between Medial VN 2 and Lateral VN 2	Mid-life participation in sports clubs or gyms	0.090	0.036	0.030	0.013	0.362
Connectivity between L CON and R CON	Mid-life participation in religious activities	-0.057	0.023	-0.031	0.014	0.371
Connectivity between AN and BN	Mid-life participation in sports clubs or gyms	-0.039	0.016	-0.030	0.014	0.372
Connectivity between Medial VN and L CON	Mid-life attendance to adult educational classes	-0.046	0.019	-0.030	0.015	0.375
Connectivity between Anterior DMN and Lateral VN 2	Mid-life attendance to adult educational classes	0.060	0.025	0.029	0.015	0.375
Connectivity between Anterior DMN 2 and AN 2	Mid-life computer use	-0.064	0.026	-0.029	0.015	0.375
Connectivity between Lateral VN and Anterior DMN 2	Mid-life participation in sports clubs or gyms	0.035	0.014	0.030	0.016	0.381
Connectivity between AN and Lateral VN 2	Mid-life participation in sports clubs or gyms	0.029	0.012	0.029	0.016	0.381
Connectivity between SMN 3 and BN	Mid-life family and friend visits	-0.046	0.019	-0.028	0.016	0.382
Connectivity between Lateral VN and AN 2	Mid-life participation in sports clubs or gyms	-0.054	0.023	-0.029	0.017	0.392
Connectivity between Posterior DMN 2 and Precuneus/PCC DMN	Mid-life attendance to social clubs or pubs	-0.062	0.026	-0.031	0.017	0.392
Connectivity between AN and AN 2	Mid-life participation in sports clubs or gyms	0.038	0.016	0.029	0.017	0.392
Connectivity between R FPN and AN 2	Mid-life attendance to social clubs or pubs	0.057	0.024	0.031	0.018	0.395
Connectivity between Lateral VN and Lateral VN 2	Mid-life attendance to adult educational classes	-0.088	0.037	-0.028	0.018	0.395
Connectivity between SMN and Posterior DMN	Mid-life computer use	-0.078	0.033	-0.028	0.018	0.395
Connectivity between SMN 2 and Precuneus/PCC DMN	Mid-life attendance to adult educational classes	0.059	0.025	0.028	0.019	0.399
Connectivity between R FPN and SMN 2	Mid-life attendance to social clubs or pubs	0.046	0.020	0.031	0.019	0.404
Connectivity between Posterior DMN 2 and Precuneus/PCC DMN	Mid-life participation in religious activities	0.065	0.028	0.029	0.020	0.409
Connectivity between Medial VN and Posterior DMN	Mid-life attendance to adult educational classes	-0.054	0.023	-0.028	0.021	0.409
Connectivity between SMN and Medial VN 2	Mid-life attendance to social clubs or pubs	0.053	0.023	0.030	0.021	0.409
Connectivity between Posterior DMN and SMN 2	Mid-life attendance to adult educational classes	0.064	0.028	0.028	0.021	0.409
Connectivity between SMN 3 and L CON	Mid-life participation in sports clubs or gyms	-0.028	0.012	-0.028	0.021	0.409
Connectivity between Medial VN 2 and L CON	Mid-life attendance to social clubs or pubs	-0.041	0.018	-0.030	0.022	0.416
Connectivity between Anterior DMN 2 and BN	Mid-life family and friend visits	0.036	0.016	0.027	0.023	0.421
Connectivity between SMN 3 and CN	Mid-life attendance to adult educational classes	0.048	0.021	0.027	0.024	0.427
Connectivity between SMN 2 and AN	Mid-life family and friend visits	0.057	0.025	0.027	0.024	0.427
Connectivity between Anterior DMN 2 and ECN	Mid-life participation in sports clubs or gyms	-0.040	0.018	-0.027	0.024	0.427
Connectivity between CN and BN	Mid-life family and friend visits	0.032	0.014	0.026	0.024	0.427
Connectivity between SMN 2 and Anterior DMN 2	Mid-life family and friend visits	0.043	0.019	0.027	0.025	0.427

Connectivity between Posterior DMN 2 and AN 2	Mid-life attendance to social clubs or pubs	0.051	0.023	0.029	0.025	0.427
Connectivity between Lateral VN and AN	Mid-life participation in religious activities	-0.036	0.016	-0.028	0.026	0.427
Connectivity between Posterior DMN and AN 2	Mid-life participation in sports clubs or gyms	0.044	0.020	0.027	0.027	0.427
Connectivity between L CON and Precuneus/PCC DMN	Mid-life attendance to adult educational classes	0.058	0.026	0.027	0.027	0.427
Connectivity between Lateral VN and SMN 2	Mid-life family and friend visits	-0.057	0.026	-0.026	0.027	0.427
Connectivity between SMN and CN	Mid-life participation in sports clubs or gyms	0.027	0.012	0.027	0.027	0.427
Connectivity between Anterior DMN and BN	Mid-life participation in religious activities	0.036	0.016	0.028	0.028	0.428
Connectivity between Posterior DMN and ECN	Mid-life participation in religious activities	-0.057	0.026	-0.028	0.028	0.432
Connectivity between Medial VN 2 and SMN 2	Mid-life participation in religious activities	0.051	0.023	0.027	0.029	0.435
Connectivity between Medial VN 2 and AN 2	Mid-life participation in sports clubs or gyms	0.049	0.023	0.027	0.029	0.435
Connectivity between R FPN and Posterior DMN	Mid-life participation in sports clubs or gyms	-0.048	0.022	-0.027	0.029	0.435
Connectivity between L FPN and ECN	Mid-life participation in sports clubs or gyms	-0.051	0.023	-0.026	0.030	0.442
Connectivity between Lateral VN and AN 2	Mid-life attendance to social clubs or pubs	0.055	0.025	0.028	0.030	0.446
Connectivity between Medial VN and AN 2	Mid-life computer use	0.058	0.027	0.026	0.031	0.450
Connectivity between Posterior DMN and SMN 2	Mid-life participation in sports clubs or gyms	0.040	0.019	0.026	0.031	0.452
Connectivity between Anterior DMN and Precuneus/PCC DMN	Mid-life attendance to social clubs or pubs	0.051	0.024	0.027	0.032	0.458
Connectivity between SMN and ECN	Mid-life attendance to social clubs or pubs	-0.049	0.023	-0.028	0.032	0.458
Connectivity between CN and R CON	Mid-life participation in religious activities	-0.027	0.013	-0.027	0.032	0.458
Connectivity between Anterior DMN 2 and ECN	Mid-life computer use	0.058	0.027	0.025	0.034	0.461
Connectivity between AN 2 and Lateral VN 2	Mid-life family and friend visits	0.052	0.025	0.025	0.034	0.461
Connectivity between L FPN and SMN 3	Mid-life attendance to social clubs or pubs	0.034	0.016	0.028	0.034	0.461
Connectivity between SMN and SMN 3	Mid-life computer use	-0.056	0.027	-0.024	0.035	0.461
Connectivity between L FPN and Posterior DMN	Mid-life computer use	-0.068	0.032	-0.025	0.035	0.461
Connectivity between Medial VN and Posterior DMN	Mid-life participation in religious activities	-0.040	0.019	-0.026	0.035	0.461
Connectivity between SMN 3 and R CON	Mid-life attendance to social clubs or pubs	-0.029	0.014	-0.027	0.035	0.461
Connectivity between Posterior DMN and L CON	Mid-life family and friend visits	-0.050	0.024	-0.025	0.035	0.461
Connectivity between Lateral VN and SMN 2	Mid-life attendance to adult educational classes	-0.066	0.031	-0.025	0.035	0.461
Connectivity between Medial VN and Medial VN 2	Mid-life attendance to adult educational classes	-0.083	0.039	-0.025	0.036	0.461
Connectivity between Posterior DMN 2 and BN	Mid-life attendance to social clubs or pubs	0.029	0.014	0.027	0.036	0.461
Connectivity between Posterior DMN 2 and Medial VN 2	Mid-life participation in sports clubs or gyms	-0.043	0.021	-0.025	0.037	0.469
Connectivity between Anterior DMN and BN	Mid-life attendance to adult educational classes	0.042	0.020	0.025	0.038	0.469
Connectivity between Posterior DMN and Precuneus/PCC DMN	Mid-life family and friend visits	-0.055	0.026	-0.024	0.039	0.469
Connectivity between Posterior DMN 2 and SMN 2	Mid-life participation in sports clubs or gyms	0.035	0.017	0.025	0.039	0.469
Connectivity between SMN 3 and R CON	Mid-life family and friend visits	0.031	0.015	0.024	0.039	0.469
Connectivity between Medial VN and L FPN	Mid-life attendance to adult educational classes	-0.046	0.022	-0.025	0.041	0.469
Connectivity between Posterior DMN 2 and Anterior DMN 2	Mid-life computer use	0.055	0.027	0.025	0.041	0.469
Connectivity between Medial VN 2 and BN	Mid-life family and friend visits	-0.033	0.016	-0.024	0.041	0.469
Connectivity between Anterior DMN and Lateral VN	Mid-life participation in sports clubs or gyms	-0.036	0.017	-0.025	0.041	0.469
Connectivity between SMN and ECN	Mid-life participation in religious activities	-0.050	0.025	-0.026	0.041	0.469
Connectivity between Anterior DMN and Medial VN 2	Mid-life family and friend visits	0.045	0.022	0.024	0.041	0.469

Connectivity between BN and Precuneus/PCC DMN	Mid-life attendance to adult educational classes	-0.037	0.018	-0.025	0.042	0.469
Connectivity between R FPN and AN 2	Mid-life participation in sports clubs or gyms	0.044	0.021	0.025	0.042	0.469
Connectivity between Anterior DMN 2 and BN	Mid-life participation in religious activities	0.031	0.015	0.025	0.043	0.469
Connectivity between AN and R CON	Mid-life attendance to social clubs or pubs	0.027	0.014	0.026	0.043	0.469
Connectivity between SMN 2 and ECN	Mid-life participation in sports clubs or gyms	0.037	0.018	0.024	0.043	0.469
Connectivity between SMN 3 and BN	Mid-life attendance to adult educational classes	-0.047	0.023	-0.024	0.044	0.469
Connectivity between SMN 2 and ECN	Mid-life participation in religious activities	-0.044	0.022	-0.025	0.044	0.469
Connectivity between L CON and Anterior DMN 2	Mid-life attendance to social clubs or pubs	0.036	0.018	0.026	0.044	0.469
Connectivity between Medial VN 2 and SMN 3	Mid-life participation in sports clubs or gyms	0.030	0.015	0.025	0.044	0.469
Connectivity between SMN 2 and CN	Mid-life attendance to adult educational classes	0.053	0.026	0.024	0.044	0.469
Connectivity between SMN and AN 2	Mid-life computer use	0.063	0.031	0.024	0.044	0.469
Connectivity between SMN and ECN	Mid-life attendance to adult educational classes	-0.061	0.031	-0.024	0.045	0.474
Connectivity between SMN and Medial VN	Mid-life participation in religious activities	-0.037	0.019	-0.025	0.046	0.475
Connectivity between SMN and SMN 3	Mid-life attendance to adult educational classes	-0.051	0.026	-0.023	0.046	0.475
Connectivity between R FPN and R CON	Mid-life participation in sports clubs or gyms	-0.046	0.023	-0.024	0.046	0.478
Connectivity between AN 2 and BN	Mid-life attendance to social clubs or pubs	-0.036	0.018	-0.026	0.047	0.484
Connectivity between Anterior DMN 2 and CN	Mid-life family and friend visits	-0.026	0.013	-0.023	0.048	0.484
Connectivity between SMN 2 and ECN	Mid-life family and friend visits	0.044	0.022	0.023	0.048	0.485
Connectivity between Anterior DMN and Posterior DMN	Mid-life participation in religious activities	0.051	0.026	0.025	0.048	0.485
Connectivity between Anterior DMN 2 and CN	Mid-life computer use	-0.033	0.017	-0.023	0.049	0.485
Connectivity between SMN 2 and Anterior DMN 2	Mid-life participation in sports clubs or gyms	0.030	0.015	0.024	0.050	0.492

Abbreviations- AN = Auditory Network; BGN= Basal ganglia network; CN = Cerebellar Network; CON = Cingulo-opercular network; DMN = Default mode network; ECN = Executive control network; FPN = Frontoparietal Network; SMN = Sensorimotor network; VN = Visual Network.
Bold = survived FDR corrections.

Appendix 5.13 Table to show the associations between weekly mid-life participation in activities and resting-state functional connectivity. Results are adjusted for sociodemographic, imaging, health and lifestyle co-variates (i.e. Model 3).

Dependent Variable	Predictor	B	SE	β	p-value	FDR q-value
Connectivity between SMN 3 and CN	Late-life participation in sports clubs or gyms	0.055	0.014	0.045	0.000	0.256
Connectivity between SMN 3 and Lateral VN 2	Late-life participation in sports clubs or gyms	0.049	0.014	0.043	0.000	0.256
Connectivity between R FPN and SMN 3	Late-life computer use	-0.110	0.031	-0.042	0.000	0.256
Connectivity between AN and AN 2	Late-life participation in sports clubs or gyms	0.055	0.016	0.042	0.001	0.256
Connectivity between AN and CN	Late-life participation in sports clubs or gyms	0.044	0.013	0.041	0.001	0.256
Connectivity between L FPN and ECN	Late-life participation in sports clubs or gyms	-0.078	0.023	-0.041	0.001	0.256
Connectivity between Anterior DMN and BN	Late-life participation in religious activities	0.052	0.016	0.040	0.001	0.337
Connectivity between Anterior DMN and Precuneus/PCC DMN	Late-life participation in sports clubs or gyms	0.068	0.021	0.038	0.001	0.345
Connectivity between SMN 2 and SMN 3	Late-life participation in sports clubs or gyms	0.074	0.024	0.037	0.002	0.345
Connectivity between Lateral VN and SMN 2	Late-life participation in religious activities	-0.076	0.025	-0.038	0.003	0.345
Connectivity between AN and SMN 3	Late-life participation in sports clubs or gyms	0.052	0.017	0.036	0.003	0.345
Connectivity between SMN 2 and Anterior DMN 2	Late-life participation in sports clubs or gyms	0.046	0.015	0.036	0.003	0.345
Connectivity between SMN 2 and ECN	Late-life attendance to adult educational classes	0.085	0.029	0.035	0.003	0.345
Connectivity between SMN and SMN 3	Late-life participation in sports clubs or gyms	-0.050	0.017	-0.035	0.003	0.345
Connectivity between Anterior DMN 2 and BN	Late-life participation in religious activities	0.044	0.015	0.036	0.004	0.345
Connectivity between Medial VN and R FPN	Late-life family and friend visits	-0.059	0.020	-0.035	0.004	0.345
Connectivity between Lateral VN and AN	Late-life participation in religious activities	-0.046	0.016	-0.036	0.004	0.345
Connectivity between Medial VN 2 and Posterior DMN	Late-life participation in sports clubs or gyms	0.053	0.019	0.035	0.004	0.345
Connectivity between L CON and R CON	Late-life attendance to adult educational classes	-0.085	0.030	-0.034	0.005	0.345
Connectivity between SMN 2 and R CON	Late-life participation in sports clubs or gyms	0.047	0.017	0.034	0.005	0.345
Connectivity between SMN and Posterior DMN	Late-life attendance to social clubs or pubs	0.067	0.024	0.036	0.005	0.345
Connectivity between Posterior DMN 2 and Medial VN 2	Late-life computer use	0.125	0.045	0.033	0.006	0.345
Connectivity between SMN 3 and Lateral VN 2	Late-life participation in religious activities	0.045	0.016	0.035	0.006	0.345
Connectivity between Medial VN and R CON	Late-life attendance to social clubs or pubs	0.039	0.014	0.036	0.006	0.345
Connectivity between SMN 3 and BN	Late-life participation in sports clubs or gyms	-0.043	0.015	-0.033	0.006	0.345
Connectivity between CN and AN 2	Late-life attendance to adult educational classes	0.065	0.024	0.033	0.006	0.345
Connectivity between AN and Lateral VN 2	Late-life attendance to social clubs or pubs	-0.037	0.013	-0.035	0.006	0.345
Connectivity between CN and ECN	Late-life family and friend visits	0.046	0.017	0.032	0.006	0.345
Connectivity between CN and Precuneus/PCC DMN	Late-life attendance to social clubs or pubs	0.039	0.014	0.034	0.006	0.352
Connectivity between R FPN and AN 2	Late-life attendance to social clubs or pubs	0.064	0.024	0.035	0.007	0.357
Connectivity between Anterior DMN and Lateral VN	Late-life participation in sports clubs or gyms	-0.047	0.017	-0.033	0.008	0.357
Connectivity between Anterior DMN and AN	Late-life attendance to adult educational classes	0.055	0.021	0.032	0.008	0.357
Connectivity between L CON and AN 2	Late-life participation in religious activities	-0.062	0.023	-0.033	0.008	0.357
Connectivity between SMN 2 and AN	Late-life participation in religious activities	0.065	0.024	0.033	0.008	0.357
Connectivity between L FPN andPrecuneus/PCC DMN	Late-life attendance to adult educational classes	0.090	0.034	0.032	0.008	0.357

Connectivity between SMN and R CON	Late-life participation in sports clubs or gyms	-0.051	0.019	-0.032	0.008	0.357
Connectivity between Medial VN and Posterior DMN	Late-life participation in religious activities	-0.050	0.019	-0.033	0.008	0.357
Connectivity between L CON and Anterior DMN 2	Late-life participation in sports clubs or gyms	0.042	0.016	0.032	0.008	0.357
Connectivity between Anterior DMN 2 and AN 2	Late-life participation in sports clubs or gyms	0.044	0.017	0.032	0.008	0.357
Connectivity between AN and AN 2	Late-life computer use	0.093	0.035	0.031	0.009	0.357
Connectivity between Medial VN and Posterior DMN	Late-life attendance to adult educational classes	-0.064	0.025	-0.031	0.009	0.357
Connectivity between Medial VN 2 and Posterior DMN	Late-life computer use	0.106	0.041	0.031	0.009	0.357
Connectivity between Posterior DMN and R CON	Late-life family and friend visits	0.064	0.025	0.031	0.010	0.363
Connectivity between Medial VN and L FPN	Late-life attendance to adult educational classes	-0.061	0.024	-0.031	0.011	0.363
Connectivity between Anterior DMN 2 and CN	Late-life family and friend visits	-0.035	0.014	-0.030	0.011	0.363
Connectivity between R FPN and SMN 2	Late-life computer use	0.097	0.038	0.030	0.011	0.365
Connectivity between AN 2 and Lateral VN 2	Late-life participation in sports clubs or gyms	0.051	0.020	0.031	0.012	0.369
Connectivity between L CON and Anterior DMN 2	Late-life computer use	-0.089	0.035	-0.030	0.012	0.369
Connectivity between Lateral VN and CN	Late-life family and friend visits	0.041	0.016	0.030	0.012	0.369
Connectivity between Lateral VN and SMN 2	Late-life attendance to adult educational classes	-0.084	0.033	-0.030	0.012	0.369
Connectivity between AN 2 andPrecuneus/PCC DMN	Late-life computer use	-0.100	0.040	-0.030	0.012	0.369
Connectivity between CN and AN 2	Late-life participation in sports clubs or gyms	0.037	0.015	0.030	0.012	0.369
Connectivity between Lateral VN and AN 2	Late-life participation in sports clubs or gyms	-0.056	0.023	-0.029	0.014	0.410
Connectivity between SMN and CN	Late-life participation in sports clubs or gyms	0.030	0.012	0.029	0.017	0.455
Connectivity between Medial VN 2 and Posterior DMN	Late-life family and friend visits	0.056	0.024	0.028	0.017	0.463
Connectivity between SMN and Anterior DMN 2	Late-life attendance to social clubs or pubs	0.042	0.018	0.030	0.018	0.483
Connectivity between ECN andPrecuneus/PCC DMN	Late-life family and friend visits	0.059	0.025	0.027	0.020	0.510
Connectivity between Posterior DMN 2 and Medial VN 2	Late-life participation in sports clubs or gyms	-0.047	0.021	-0.028	0.021	0.517
Connectivity between Medial VN and SMN 2	Late-life attendance to adult educational classes	-0.058	0.026	-0.028	0.022	0.538
Connectivity between SMN andPrecuneus/PCC DMN	Late-life attendance to social clubs or pubs	0.050	0.022	0.029	0.023	0.542
Connectivity between SMN 3 and Anterior DMN 2	Late-life computer use	-0.059	0.026	-0.027	0.023	0.542
Connectivity between Posterior DMN 2 and Lateral VN 2	Late-life participation in sports clubs or gyms	-0.039	0.017	-0.028	0.024	0.545
Connectivity between R FPN and R CON	Late-life attendance to social clubs or pubs	-0.057	0.025	-0.029	0.024	0.545
Connectivity between Posterior DMN and SMN 3	Late-life attendance to social clubs or pubs	-0.032	0.014	-0.029	0.026	0.562
Connectivity between Lateral VN and R FPN	Late-life attendance to adult educational classes	0.066	0.030	0.027	0.026	0.562
Connectivity between Posterior DMN 2 and ECN	Late-life participation in sports clubs or gyms	-0.050	0.023	-0.027	0.027	0.564
Connectivity between SMN and Posterior DMN	Late-life computer use	-0.111	0.050	-0.026	0.027	0.564
Connectivity between Anterior DMN and Lateral VN	Late-life attendance to social clubs or pubs	0.043	0.019	0.028	0.027	0.564
Connectivity between L CON and BN	Late-life participation in religious activities	-0.031	0.014	-0.028	0.028	0.564
Connectivity between SMN 3 and AN 2	Late-life participation in sports clubs or gyms	0.038	0.017	0.027	0.028	0.566
Connectivity between Medial VN 2 and AN 2	Late-life computer use	0.108	0.050	0.026	0.030	0.601
Connectivity between SMN 3 and L CON	Late-life participation in sports clubs or gyms	-0.026	0.012	-0.026	0.031	0.602
Connectivity between Posterior DMN and AN 2	Late-life participation in sports clubs or gyms	0.043	0.020	0.026	0.031	0.602
Connectivity between Anterior DMN and CN	Late-life attendance to adult educational classes	-0.044	0.021	-0.026	0.032	0.602
Connectivity between SMN 3 and Precuneus/PCC DMN	Late-life attendance to adult educational classes	0.046	0.021	0.026	0.034	0.623

Connectivity between AN and AN 2	Late-life participation in religious activities	0.041	0.019	0.026	0.034	0.624
Connectivity between Medial VN 2 and SMN 3	Late-life participation in sports clubs or gyms	0.032	0.015	0.026	0.035	0.624
Connectivity between Medial VN 2 and L CON	Late-life attendance to social clubs or pubs	-0.037	0.018	-0.027	0.035	0.624
Connectivity between Anterior DMN 2 and Precuneus/PCC DMN	Late-life computer use	0.083	0.040	0.025	0.036	0.624
Connectivity between L FPN and R CON	Late-life attendance to adult educational classes	0.091	0.044	0.025	0.036	0.624
Connectivity between AN and Lateral VN 2	Late-life computer use	-0.055	0.027	-0.025	0.038	0.646
Connectivity between R FPN and Medial VN 2	Late-life attendance to social clubs or pubs	0.046	0.022	0.027	0.038	0.651
Connectivity between R FPN and ECN	Late-life participation in sports clubs or gyms	0.047	0.023	0.025	0.040	0.652
Connectivity between R FPN and CN	Late-life attendance to adult educational classes	-0.041	0.020	-0.025	0.042	0.666
Connectivity between L CON and Precuneus/PCC DMN	Late-life computer use	-0.079	0.039	-0.024	0.042	0.666
Connectivity between R FPN and L CON	Late-life attendance to social clubs or pubs	0.052	0.025	0.026	0.042	0.666
Connectivity between Anterior DMN and CN	Late-life computer use	-0.058	0.028	-0.024	0.043	0.674
Connectivity between SMN 2 and CN	Late-life attendance to adult educational classes	0.057	0.028	0.024	0.044	0.674
Connectivity between AN and Precuneus/PCC DMN	Late-life computer use	0.055	0.027	0.024	0.044	0.674
Connectivity between Medial VN 2 and BN	Late-life participation in religious activities	-0.031	0.016	-0.025	0.046	0.698
Connectivity between Posterior DMN and SMN 2	Late-life computer use	-0.081	0.041	-0.024	0.047	0.701
Connectivity between Posterior DMN 2 and Medial VN 2	Late-life participation in religious activities	-0.049	0.025	-0.025	0.048	0.701
Connectivity between AN and Lateral VN 2	Late-life participation in sports clubs or gyms	0.024	0.012	0.024	0.048	0.701
Connectivity between SMN and ECN	Late-life attendance to social clubs or pubs	-0.045	0.023	-0.025	0.048	0.701
Connectivity between AN and CN	Late-life participation in religious activities	0.031	0.016	0.025	0.048	0.701
Connectivity between Posterior DMN 2 and AN 2	Late-life attendance to adult educational classes	-0.064	0.032	-0.024	0.049	0.701
Connectivity between R FPN and Anterior DMN 2	Late-life participation in sports clubs or gyms	-0.035	0.018	-0.024	0.049	0.701
Connectivity between R FPN and R CON	Late-life participation in religious activities	0.054	0.027	0.025	0.049	0.701

Abbreviations- AN = Auditory Network; BGN= Basal ganglia network; CN = Cerebellar Network; CON = Cingulo-opercular network; DMN = Default mode network; ECN = Executive control network; FPN = Frontoparietal Network; SMN = Sensorimotor network; VN = Visual Network.
Bold = survived FDR corrections.