# Exploring the Complexity of Healthy Aging: A Multi-Time-Scale Analysis to Investigate the Reorganization of Functional Networks and Associated Cognitive Changes across the Lifespan

Thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science in Computational Natural Sciences by Research

by

Arpita Dash 20161048 arpita.dash@research.iiit.ac.in



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# International Institute of Information Technology Hyderabad, India

# CERTIFICATE

It is certified that the work contained in this thesis, titled "Exploring the Complexity of Healthy Aging: A Multi-Time-Scale Analysis to Investigate the Reorganization of Functional Networks and Associated Cognitive Changes across the Lifespan" by Arpita Dash, has been carried out under my supervision and is not submitted elsewhere for a degree.

Date

Advisor: Prof. Bapi Raju Surampudi

To those who stood by my side, To everyone who believed in me, This is for you.

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### Abstract

"Your brain is constantly rewiring itself, adapting with each new experience. It's a dynamic, ever-changing network of connections, shaped by the world around you." - David Eagleman

This thesis investigates the reorganization of brain networks during the aging process, particularly in the transition from young to middle-aged to older adults. The study utilizes the CAMCAN dataset, a comprehensive cross-sectional dataset with multimodal data, including pre-processed resting-state fMRI (rs-fMRI) data. The aim is to understand how brain networks evolve with age and identify key brain regions and network properties that undergo changes. Data-driven statistical and graph-theoretic measures are employed to study modular segregation and integration in the brain.

The results reveal characteristic nodes forming stable cores and flexible peripheries in both young and old age groups. Notably, regions within the Default Mode network (DMN) show a negative correlation with modularity in the old age group, while regions from the Limbic, SensoriMotor (SMN), and Salience networks display a positive correlation. Machine learning models based on flexibility scores further validate the relevance of these regions, providing promising insights for future investigations.

Additionally, the study uncovers age-related changes in brain connectivity and network properties. Modularity increases with age, indicating greater functional specialization in the aging brain, accompanied by a decrease in flexibility, suggesting reduced adaptability to changing cognitive demands. The negative correlation between flexibility and modularity across all age groups implies that as the brain becomes less modular, it becomes more flexible in its organization. Certain brain regions show significant connectivity alterations, with increased participation coefficient in some frontal and temporal regions and decreased participation coefficient in several frontal and parietal regions. Hemispheric differences indicate that age-related connectivity changes may vary between hemispheres.

Furthermore, the complexity of the relationship between cognitive abilities, task performance, and brain network dynamics is highlighted. The absence of strong correlations between task scores and network measures at the nodal level, along with the weak correlation between Cattell scores and global flexibility, underscore the multifaceted nature of these associations. Age alone cannot fully account for the observed dynamics, suggesting the involvement of other factors in shaping the relationship between cognition and brain network measures.

However, this study has limitations. The use of cross-sectional data hinders the exploration of individual changes over time, and longitudinal data would provide more robust insights. The dataset's relatively small size and the categorization of age into discrete groups may limit the generalizability of the findings. Moreover, relying solely on resting-state fMRI data may not fully capture the dynamic nature of brain function during various cognitive processes. Additionally, causal inferences should be made with caution, as the study is based on observational data, and other factors may influence the observed brain network changes.

In conclusion, this thesis contributes to understanding age-related changes in brain networks and their impact on cognitive aging. The findings highlight the importance of specific brain regions in maintaining functional networks during aging and underscore the complexity of brain network dynamics. Addressing the limitations in future research will enhance our knowledge of brain aging and the interplay between brain networks, cognitive abilities, and behavior.

# Contents

Ch	apter	P	age			
1	Intro	duction	1			
	1.1	Motivation	1			
	1.2	What happens to the brain when one ages?	1			
	1.3	What are the challenges in the field?	2			
	1.4	Contributions of this Thesis	2			
	1.5	Thesis Workflow	3			
2	Defir	nitions and Methodologies	5			
	2.1	Methods to characterize brain function and structure	5			
		2.1.1 Stimulation-based function characterization	5			
		2.1.2 Neuroimaging modalities	5			
	2.2	Resting state vs Task based data	6			
	2.3	CAMCAN dataset	7			
		2.3.1 Choice of participants	7			
		2.3.2 Data acquisition and preprocessing	7			
		2.3.3 Task scores	7			
	2.4	Modelling the brain function - Graph Theory	8			
		2.4.1 Static Functional Connectivity	8			
		2.4.2 Dynamic Functional Connectivity	9			
		2.4.3 Network measures	9			
	2.5	Statistical Analysis methods	14			
	2.6	Identifying important features - ML approach	14			
		2.6.1 Feature Selection and Reduction	15			
		2.6.2 Choice of classfier	15			
	2.7	Regression analysis	16			
3	Related Work					
	3.1	Structural changes with age	19			
	3.2	Functional changes with age	21			
	3.3	Behavioural and cognitive changes with age	24			
	3.4	Theories of ageing	25			
	3.5	Challenges in current methodologies	28			

### CONTENTS

4	Char	acterizi	ng the Dynamic Reorganization in Healthy Ageing - Young vs Old	0
	4.1	Introdu	action	1
	4.2	Materi	als and Methods	2
		4.2.1	Participants	2
		4.2.2	Data acquisition and preprocessing	2
		4.2.3	Modeling the functional connectivity	2
			4.2.3.1 Static Functional Connectivity	2
			4.2.3.2 Dynamic Functional Connectivity	3
		4.2.4	Network measures	3
			4.2.4.1 Modularity 3'	3
			4.2.4.2 Multilaver Modularity Maximization Algorithm	3
			4243 Flexibility 34	4
		425	Statistical Analysis	4
		1.2.5	4.251 Age effects on flexibility $34$	1 4
			4.2.5.2 Modularity and flexibility relation	т 5
		126	Classification 24	5 5
		4.2.0	Classification	5 5
			4.2.0.1 Feature Selection / Reduction	5 5
	1 2	Decult	4.2.0.2 Choice of classifier	s c
	4.3			3 7
		4.3.1	Modularity and Age	0 6
		4.3.2	Modularity vs Global Flexibility	5
		4.3.3	Modularity vs High/Low Node flexibility	/
		4.3.4	Network-level changes across age	7
		4.3.5	Classification	0
		4.3.6	Overlap with Network Statistics	0
	4.4	Conclu	$asion \dots \dots$	1
5	Char	acterizi	ng Age-Related Functional Changes and their Association with Cognitive Performance:	
	A G	raph The	eory Approach	4
	5.1	Introdu	144 Inction	4
	5.2	Metho	ds	5
		5.2.1	Network measures	5
		5.2.2	Correlation between network measures	6
		5.2.3	Calculating the task scores	6
		524	Choice of regression model 40	6
		525	Correlation between task scores and network measures 4'	7
	53	Results		, 7
	0.0	531	Modularity changes on age 4'	, 7
		532	Node-level changes in flevibility	' 7
		533	Network-level changes in flexibility with age	'n
		531	Participation coefficient changes with age	ó
		525	Within modulo degree 7 score (WMD) across age groups	י 1
		5.5.5 5.2.4	Correlation between dynamic and static network measures	ר ר
		5.5.0	Conclation between dynamic and static network measures	2 7
		J.J./	Changes in provincial hubs across age	ו ר
		J.J.ð	Changes in connector nuos across age	/ 0
		5.5.9	memispherical asymmetry in regions with ageing	I

# CONTENTS

		5.3.10	Age-related changes in task-scores	59
		5.3.11	Relation between network measures and cognitive performance	59
	5.4	Discus	sion	61
		5.4.1	Modularity vs Global Flexibility	61
		5.4.2	Node-level changes in flexibility	62
		5.4.3	Network-level changes in flexibility across age	64
		5.4.4	Network flexibility vs Modularity	64
		5.4.5	Participation coefficient	65
		5.4.6	Within-Module z-degree	68
		5.4.7	Provincial hubs	71
		5.4.8	Connector Hubs	71
		5.4.9	Hemispherical asymmetry in activations	71
		5.4.10	Task scores with age	72
		5.4.11	Relation between task scores and network measures of rs-fMRI	72
	5.5	Conclu	sion	73
6	Cone	clusion a	and Future Work	77
	6.1	Conclu	sion	77
	Appe	endix A:	Appendix A	79
Bi	bliogr	aphy .		104

# List of Figures

Figure		Page
2.1 2.2	Overview of the Louvain algorithm	12 13
3.1 3.2	Surface plots of Resting State Networks	23 26
4.1 4.2 4.3 4.4 4.5 4.6	Modularity scores of participants across age groups	36 37 38 39 40 41
5.1	Modularity vs Age Regression fit	48
5.2	Network changes in flexibility scores across age group	50
5.3	Network-wise Comparison of Participation Coefficient across Age Groups	51
5.4	Network Average Within-Module Degree (z-score) Across Young, Middle, and Old Age	
	Groups	52
5.5	Modularity vs Global Flexibility	53
5.6	Correlation Between Network-Averaged Participation Coefficient and Flexibility Across	
5.7	All Ages	55
	across All Ages	56
5.8	Analysis of Provincial Hubs' Age Categories	58
5.9	Analysis of Connector Hubs' Age Categories	58
5.10	Relationship between Cattell and Benton Task Scores and Age	60
5.11	Regression Residuals in Relation to Task Performance and Network Measures	61
5.12	Correlation between Modularity and Flexibility in Networks Among Young Age Groups	62
5.13	Correlation between Global and Network-Wise Flexibility with Modularity in the Mid- dle Age Group	63
5.14	Correlation between Global and Network-Wise Flexibility with Modularity in the Old	
	Age Group	63
5.15	Network-Level Correlation between Flexibility and Participation Coefficient in the Young	- ,
	Age Group	65

5.16	Network-Level Correlation between Flexibility and Participation Coefficient in the Mid-	
	dle Age Group	66
5.17	Network-Level Correlation between Flexibility and Participation Coefficient in the Old	
	Age Group	67
5.18	Network-Wise Flexibility Correlation with Within-Module Degree Z-Score in the Young	
	Age Group	68
5.19	Network-Wise Flexibility Correlation with Within-Module Degree Z-Score in the Mid-	
	dle Age Group	69
5.20	Network-Wise Flexibility Correlation with Within-Module Degree Z-Score in the Old	
	Age Group	70
A.1	Within-Module Degree and Participation Coefficients of Nodes with Significant Age-	
	Related Differences in WMD Scores	89
A.2	BrainNet Visualization of the flexibility of the nodes that show age effect and are sig-	
	nificantly different across age groups.	92
A.3	Brain Regions with Significant Differences in Participation Coefficients across Age	
	Groups	93

# List of Tables

Table		Page
4.1	Classifier Models and Accuracy scores	42
4.2	Comparison of features and related performance while using SVM to classify into age	12
4.3	Common features discovered by ML model and Network Statistics	42 43
5.1	Partial Correlations between Global Network Measures and Task Performance Scores,	
	Controlling for Age	74
5.2	Best fit of Regression Models	75
5.3	Mutual Information (MI) and Normalized Mutual Information of Participation Coeffi-	
5.4	Table illustrating the mutual information (MI) and normalized mutual information val- ues of within-module degree z-score calculated between different age groups. The mu- tual information represents the association between Group 1 and Group 2, while the	75
	normalized value is calculated across the focused group, Group 1	76
A.1	Brain Regions with Significant Age-Related Differences in Flexibility Values.	79
A.2	Nodes with High Flexibility in the Young Age Group	81
A.3	Nodes with High Flexibility in the Middle Age Group	82
A.4	Nodes with High Flexibility in the Old Age Group	83
A.5	Brain Regions with Significant Differences in Participation Coefficient across Age Group	s 84
A.6	Brain Regions with Significant Differences in Within-Module Degree z-score across	
	Age Groups	85
A.7	Brain Regions with Significant Difference in Both Participation Coefficient and Within-	
	Module Degree z-score across Age Groups	86
A.8	Identification of Connector Hubs in the Network.	87
A.9	Identification of Provincial Hubs in the Network.	88
A.10	Correlation of Nodal Flexibility with Benton (Visual Perception and Memory) and Cat-	0.4
A 11	tell (Fluid Intelligence) Task Scores.	94
A.11	and Cattell (Fluid Intelligence) Task Scores	97
A.12	Correlation of Within-Module Degree z-score with Benton (Visual Perception and Mem-	-
	ory) and Cattell (Fluid Intelligence) Task Scores	99
A.13	Connector Hubs: Correlation of Participation Coefficient and Within-Module Degree	
	z-score with Benton and Cattell Task Scores	101

A.14 Provincial Hubs: Correlation of Participation Coefficient and Within-Module Degree	;
z-score with Benton and Cattell Task Scores.	. 102

# Chapter 1

# Introduction

### 1.1 Motivation

Ageing is an inevitable process that leads to wisdom and serenity, but it also causes the body to deteriorate faster than it can regenerate. In the brain, this deterioration is accelerated by neurological disorders like Parkinson's and Alzheimer's. As the global population ages, it becomes increasingly important to find ways to maintain the cognitive and physical health, of both the brain and the body, of older individuals and ensure their overall well-being. If we can comprehend the underlying mechanisms of these age-related changes, particularly in healthy ageing, we can develop interventions to slow down or prevent cognitive decline in ageing populations. Furthermore, studying how the healthy brain ages can help us identify possible deviations, enabling early intervention in the case of diseases. Overall, neuroscience research can provide valuable insights into the changes that occur in the ageing brain and potential ways to address them.

### **1.2** What happens to the brain when one ages?

As individuals age, the brain undergoes various changes in its structural and functional organization, which can affect cognition and overall brain health. Genetic factors, lifestyle choices, and environmental influences influence these changes. It is important to note that while some changes are commonly observed with age, there is considerable individual variability in the ageing process.

Structurally, the brain undergoes several alterations with age. One of the most noticeable changes is decreased brain volume, particularly in regions such as the prefrontal cortex, hippocampus, and cerebellum. These reductions in volume are often associated with declines in cognitive functions such as memory, attention, and executive functioning. Additionally, age-related changes in white matter integrity and connectivity have been observed, which may contribute to slower information processing and cognitive decline [1, 2, 3, 4, 5, 6, 7, 8].

Functionally, ageing is associated with changes in neural activity and activation patterns. Neuroimaging studies have revealed that older adults often show reduced brain activity during cognitive tasks compared to younger individuals. This decline in neural efficiency may reflect compensatory mechanisms or neural reorganization to maintain cognitive performance. However, it is important to note that older adults can still exhibit remarkable cognitive resilience and adaptability, and some cognitive abilities may remain stable or even improve with age [9, 10, 11, 12, 8, 13, 14, 15, 16, 17, 18].

Cognition is a complex process encompassing various domains, such as attention, memory, language, and problem-solving. With age, cognitive abilities tend to show a pattern of decline, albeit with significant individual differences. For example, processing speed tends to decrease, making analysing and responding to information more challenging. Working memory capacity may also decline, affecting the mind's ability to hold and manipulate information. However, certain types of knowledge and expertise, such as vocabulary and crystallized intelligence, can remain relatively stable or even improve over time [19, 20, 21, 22, 23, 10, 24, 25, 26, 27, 28].

# **1.3** What are the challenges in the field?

There are several challenges faced in the current literature on ageing and brain reorganization. One major challenge is the lack of standardization in the methods used to study brain structure and function. Different studies use different techniques and measures, making it difficult to compare findings across studies [29, 30].

Another challenge is the complexity of the ageing process and its effects on the brain. Ageing affects different brain regions and networks in different ways, and a range of factors, such as genetics, lifestyle, and environmental factors, influences the changes [31]. Furthermore, there is an increased risk of ageing-related neurodegenerative diseases, making distinguishing between normal ageing and pathology difficult. This complexity makes it difficult to identify clear patterns and mechanisms underlying brain ageing [32].

There is also a need for longitudinal studies that track brain changes over time to understand better the progression of ageing and its effects on the brain. Most studies are cross-sectional, meaning they only capture a snapshot of brain structure and function at a particular point in time [33].

Finally, there is a need for more diverse samples in research on brain ageing. Most studies have focused on Western, educated, industrialized, rich, and democratic (WEIRD) populations, which may not represent the global population [32] [34]. This limits the generalizability of findings and hinders efforts to address health disparities related to brain ageing.

### **1.4** Contributions of this Thesis

A significant challenge encountered in current literature is the use of diverse brain parcellations and functional connectivity metrics, leading to difficulties in comparing findings across studies. To overcome this challenge, we adopted a widely accepted brain parcellation scheme (AAL-116) and employed a standardized functional connectivity metric (Pearson correlation). Furthermore, we specifically investigated static functional connectivity networks, as well as dynamic connectivity networks, enabling us to examine whole-brain reorganization across various timescales, ranging from seconds to years. Furthermore, we investigated the relationship between modularity, flexibility, participation coefficient and within-module degree z-scores to provide insights into the brain's ability to maintain segregation and integration. We also bridge the gap between static and dynamic functional connectivity and identify the changes in the functional reorganization across different time-scales. We also investigated the important regions that are key to distinguishing brain organization across age groups. The nodes important for classification have been shown to overlap with those uncovered by data-driven statistical measures. Finally, we also explored the relation between age related decline in cognitive performance and restingstate network measures. These approaches make our study unique and provide a more comprehensive understanding of the brain's functional organization and dynamics across the lifespan.

- 1. This study used the Cam-CAN dataset to explore modular reorganization and identify nodes that make up the stable core and flexible periphery in young and old age groups using dynamic measures like flexibility. Results suggest that nodes exhibiting higher flexibility in older age groups are negatively correlated with modularity, while networks responsible for higher-order cognitive functions make up a stable core with low flexibility scores. Using node flexibility scores as features for binary classification, the Support Vector Machine with Gaussian kernel gave the best results, and the important features identified in classification align with those found through datadriven network measures analysis.
- 2. The findings in this study revealed age-related changes in network measures, with older adults showing reduced global efficiency, increased local efficiency, and decreased modularity compared to younger adults. Further, the relation between age related decline in cognitive performance and resting-state network measures were explored.

Overall, both studies suggest that the brain undergoes compensatory mechanisms to maintain cognitive function in the face of these changes, with some regions increasing connectivity to support cognitive function. In contrast, others decrease in connectivity and contribute to age-related declines in cognitive function. Most importantly, they highlight the importance of understanding age-related changes in brain connectivity to better understand the mechanisms underlying age-related cognitive decline and identify potential targets for interventions to support cognitive function in ageing.

## **1.5 Thesis Workflow**

Chapter 2 is the literature review and methodology section. The purpose of this chapter is to provide a detailed account of the methods used to conduct the research and explain the rationale for using these methods. In this chapter, the various methodologies used in the work done is introduced and explained.

This includes descriptions of experiments, data collection and analysis techniques, statistical methods, and other methodologies relevant to the research question.

Chapter 3 provides an overview of the current literature and various theories of ageing. This chapter includes an explanation of the current state of research in the field of ageing, a review of relevant literature on the topic, and a discussion of the major theories that have been proposed to explain the ageing process. The purpose of this chapter is to provide a comprehensive overview of the current state of knowledge in the field and contextualize the research question within the broader field of ageing.

Chapters 4 and 5 constitute the primary work done as a part of the thesis and present the research results. These chapters include descriptions of the experiments or data collection techniques used and analyses of the data collected. The chapters provide a detailed account of the research findings and explain how these findings contribute to the overall understanding of the research question. These chapters also include a discussion of the implications of the findings for future research and recommendations for future studies.

# Chapter 2

### **Definitions and Methodologies**

The aim of this chapter is to offer a comprehensive explanation of the techniques utilized to carry out the research, along with the reasoning behind their selection. The chapter provides an introduction and description of the different methodologies employed in literature as well as in the studies documented, which encompass statistical methods, data collection and analysis techniques, and other relevant approaches in this thesis's scope.

# 2.1 Methods to characterize brain function and structure

The subsequent subsections outline different methods presently utilized for capturing neural activity.

### 2.1.1 Stimulation-based function characterization

There are various invasive and non-invasive methods to study brain functionality. Invasive measures involve inserting electrodes into the brain and measuring reactions to electric stimulation. Some examples of invasive methods are deep brain stimulation (DBS) and motor cortex stimulation (MCS) [35]. However, due to the irreversible damage to the neurons caused by invasive methods, non-invasive methods like transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) have become popular [36].

#### 2.1.2 Neuroimaging modalities

There are many neuroimaging modalities to choose from that are based on various ways to measure brain activity. Some of the popular ones are:

 Functional Magnetic Resonance Imaging (fMRI): This technique gauges the blood oxygen leveldependent (BOLD) contrast. It relies on detecting variations in local blood flow, which results in discrepancies between oxyhemoglobin and deoxyhemoglobin levels. fMRI is widely employed for precisely mapping extensive functional networks within the brain. Nevertheless, there is a compromise between spatial and temporal resolution in this method. Certain drawbacks include the requirement for minimal head movement during scanning, susceptibility to physiological noise, limited temporal resolution, and so on. [37].

- Electroencephalogram (EEG): As neurons communicate through electrical impulses, this method relies on the brain's electrical activity. It offers a remarkably high temporal resolution in the millisecond range but exhibits limited spatial resolution due to the placement of electrodes in specific locations. However, an important drawback of this approach is that it provides relative differences between brain locations rather than an absolute measure [38, 39].
- Magnetoencephalogram (MEG): This method utilizes the magnetic field generated by electric currents in the brain to gather information about its structure and function. By identifying the sources of these magnetic fields, both spatial and temporal resolutions are significantly improved compared to EEG. MEG serves as a reference-free direct measure of brain activity and does not exhibit operational noise like fMRI. However, a significant drawback of MEG is that the signal it captures is inherently weak, which makes it susceptible to interference from background signals. To mitigate this, special shielding techniques may need to be employed to minimize external influences on the measurements [40, 41].
- Other measures: Other measures that involve more complicated methods include Positron Emission Tomography (PET), Diffusion Optical Tomography (DOT), Functional Ultrasound Imaging, etc. [42] [43][44] [45].

Due to the high spatiotemporal resolution of the fMRI modality that can throw light on the large-scale brain activity and engagement of a large number of areas. Hence, this is an ideal choice for functional connectivity creation and identification of large scale brain networks [46] [37].

# 2.2 Resting state vs Task based data

Task-based functional magnetic resonance imaging (fMRI) is a widely used approach for investigating brain activity related to specific stimuli or tasks. It involves designing experimental paradigms that elicit neural responses in response to targeted stimuli or cognitive demands. By analyzing the blood oxygen level dependent (BOLD) signal during task performance, researchers can identify brain regions and networks associated with the task and make inferences about their functional roles [42]. Restingstate fMRI, on the other hand, captures brain activity during periods of rest or when participants are not engaged in any specific task. Participants are typically instructed to relax and keep their eyes open or fixed on a point while lying in the scanner. Unlike task-based fMRI, resting-state fMRI does not involve external stimuli or explicit tasks. Instead, it reflects the intrinsic functional organization of the brain and its spontaneous activity [47, 48]. Studies have demonstrated that resting-state fMRI captures approximately 80% of the functional architecture observed in task-based fMRI.[49] [50][51].

## 2.3 CAMCAN dataset

The CAMCAN dataset chosen is a cross-sectional dataset that is available on request. In the following subsections, we describe the criteria of selection of the participants and the data acquisition and pre-processing pipelines that were used. The data that was available was already pre-processed, mapped onto AAL116 atlas and available as the BOLD signal timeseries for each of the individual regions.

#### 2.3.1 Choice of participants

The second stage of the Cam-CAN project provided the data used in this study, which can be accessed at http://www.mrc-cbu.cam.ac.uk/datasets/camcan [52]. Cam-CAN is a comprehensive cross-sectional study that involves a large-scale collection of multimodal data. The dataset includes raw and pre-processed data from structural MRI, functional MRI (fMRI), Magnetoencephalogram (MEG), behavioral scores, demographic information, and neuropsychological data. Stage 1 of the project included 3000 participants. A subset of 637 participants was selected for this study based on the criteria of being cognitively healthy (MMSE score 25) and having no history of drug abuse or current drug use. The study was conducted in accordance with the Helsinki Declaration and was approved by the Cambridgeshire 2 Research Ethics Committee. The participants were divided into three age groups: young (size: 183, mean age:  $31 \pm 6$ ), middle-aged (size: 201, mean age:  $50.5 \pm 6$ ), and old (size:253, mean age: 73).

#### 2.3.2 Data acquisition and preprocessing

The resting-state fMRI data used in the study were collected at the Medical Research Council Cognition and Brain Sciences Unit, using a 3T Siemens TIM Trio scanner with a 32-channel head coil. The acquisition parameters included: TR = 1970 ms, TE = 30 ms; voxel size =  $3.0 \times 3.0 \times 3.7$  mm; flip angle = 78°; acquisition time = 8 min 40 s, the total number of volumes = 261; 32 axial slices per volume (slice thickness 3.7mm, an interslice gap of 20%) acquired in descending order [52]. The Cam-CAN research consortium provided the preprocessed data. The anatomical Automatic Labelling atlas (AAL) was used for parcellating the brain into 116 regions, and their mean BOLD time-series signals were calculated. [53, 54].

#### 2.3.3 Task scores

2 tests were considered to account for fluid and crystallized intelligence.

The **Benton Test of Facial Recognition** [55] was considered for crystallized intelligence. It is a measure of the ability to match pictures of unfamiliar faces. It assesses the capability to recognize newly-seen faces rather than familiar ones. The short form of the Benton Test was used in the CAMCAN study, consisting of 27 trials where participants are shown a target face and an array of six faces. The

task is to identify one or more instances of the target face among the array. The total score is based on the number of correct responses, with a maximum score of 27.

The **Cattell Culture Fair, Scale 2 Form A** [56, 57] was used to assess fluid intelligence. It includes four subtests with nonverbal puzzles: series completion, classification, matrices, and conditions. Each subtest has a specific time limit, and participants are given instructions and examples before each subtest. The test is completed using a pen-and-paper format, with participants selecting responses from multiple choices and recording them on an answer sheet. The total score is based on the number of correct responses, with a maximum score of 46. [58]

### **2.4 Modelling the brain function - Graph Theory**

Graph theory has gained widespread usage in neuroscience literature for modelling the brain and drawing network-level inferences about its structure and function. The brain can be conceptualized as a network-like architecture, making it suitable for graph-based analysis. In functional modelling, regions of interest (ROIs) are represented as nodes, and the edges represent the level of coactivation or functional synchronization between them. For structural modelling, nodes correspond to anatomical regions (ROIs), while the edges signify the thickness of white matter tracts connecting the regions. Researchers can easily track the architecture and evolution of brain reorganization by employing various graph theory algorithms and measures. This can be examined at different scales, including global (whole-brain), mesoscale (network-level), and local (nodal) levels [59, 60, 61]. In the subsequent studies, we use Pearson's correlation to quantify the strength of functional connectivity between brain regions. Pearson's correlation coefficient calculates the degree of synchronized activity or functional connectivity by analyzing the time series data of two regions.

#### 2.4.1 Static Functional Connectivity

A simple and efficient approach to depict the functional connectivity between nodes (ROIs) is to calculate the mean Pearson's correlation of the BOLD signal fluctuations throughout the entire scanning duration. This method provides insights into the network-level architecture of the brain's stable organizational pattern over an extended period. However, this representation of brain functional connectivity lacks temporal information, as the correlation values are averaged across the entire scan time and do not account for dynamic changes over time.[51]

#### **ROI to Network Mapping**

The AAL atlas is a widely used brain parcellation scheme that provides standardized regions of interest. In our study, we utilized the resting-state network that was previously mapped to the corresponding brain regions as described in the work cited [62]. To ensure the reliability and validity of our findings, we also cross-validated the regions and their corresponding network mapping using the latest literature, specifically relying on the AAL atlas.

#### 2.4.2 Dynamic Functional Connectivity

While the static FC gives us insight into the architecture of the networks that remain stable over time, the non-trivial dynamics are hidden [63, 64]. The tapered sliding window method is a commonly used approach for examining dynamic functional connectivity in functional magnetic resonance imaging (fMRI) data. It involves dividing the fMRI time series into shorter, overlapping segments known as windows and estimating functional connectivity within each window. The use of tapered windows helps mitigate the abrupt transition artifacts at the edges of the windows.

One commonly employed tapered sliding window method is the Gaussian window, where the weights gradually decrease from the center of the window towards the edges. This tapering effect ensures smoother transitions and reduces the impact of abrupt changes in connectivity estimation between adjacent windows [65]. Choosing an appropriate window size is crucial for accurately capturing dynamic changes in functional connectivity. A window that is too short may not capture meaningful connectivity dynamics, while a too long window may oversimplify temporal variations or mask transient connectivity ity patterns. The optimal window size depends on several factors, including the temporal properties of the phenomenon under investigation and the fMRI acquisition parameters. For the dynamic functional connectivity (dFC) analysis, we used a tapered sliding window approach and represented the entire time series in windows of 44 seconds and a stride of 5 seconds based on the strategies followed in [66, 67, 68, 69].

#### 2.4.3 Network measures

Complex networks often have diverse structural and functional features that can be characterized by various measures. Two important categories of measures that are frequently used are measures of integration and segregation. Integration measures quantify how effectively information can flow across different modules or clusters of the network. In contrast, segregation measures describe the extent to which the network is divided into functionally distinct communities or subgroups.

- Common **measures of integration** include global efficiency and participation coefficient, which are based on the number of connections that flow through a specific node in the network. Global efficiency quantifies how efficiently the information can be transferred across the entire network, whereas participation coefficient characterizes the extent to which a particular node is involved in multiple communities or subgroups within the network [70].
- Segregation measures, on the other hand, focus on the extent to which the network is divided into subgroups that perform specialized functions. Segregation enables the network to process

information in a distributed manner, which reduces the overall wiring cost and improves the network's efficiency. An example of a measure of segregation is modularity, which quantifies the extent to which the network is divided into tightly-knit subgroups or modules [70].

Complex small-world networks, common in many natural and artificial systems, are characterized by efficient integration and segregation. These networks are composed of densely connected subgroups or modules, but they also have relatively short paths between nodes that enable efficient information transfer across the entire network.

In addition to these static measures, **dynamic measures** can also characterize how network properties change over time. One such dynamic measure that can be used to study the evolution of network structure over time or to track changes in the network's functional properties is flexibility [70].

Measures used in the upcoming work are explained in detail in the following subsections.

#### Within-Module degree

Within-module degree z-score is a static measure of centrality that is a localized, within-module form of degree centrality [70]. If a node has a high within-module degree z-score, it has a high number of edges between the nodes within the same module that it is assigned to. For a node i, the within-module degree z-score, z, is calculated as,

$$z_{i} = \frac{k_{i}(m_{i}) - k(m_{i})}{\sigma^{k(m_{i})}}$$
(2.1)

where  $k_i(m_i)$  is the number of edges between *i* and all the other nodes in  $m_i$  (within-module degree),  $\overline{k}(m_i)$  is the mean of the within-module  $m_i$  degree distribution, and  $\sigma^{k(m_i)}$  is the standard deviation of the within-module degree distribution for the module  $m_i$  [70, 71, 72]. The module/community assignment for all the ROIs must be provided to calculate the within-module degree z-score. Hence for each iteration of the community detection based on the Louvain algorithm, a corresponding WMD-z-score is calculated, as shown below,

$$Z_i = \sum_{iter \in total_{iter}} (z_{i,iter})$$
(2.2)

where  $z_{i,iter}$  is the z-score of node *i* in iteration *iter*, and *total<sub>iter</sub>* is the total number of iterations performed by the Louvain community detection algorithm. The average z-score,  $Z_i$ , was then considered the final measure of localized degree centrality.

#### **Participation coefficient**

A complementary measure to within-module degree is the participation coefficient as it captures the diversity of connections of the node in question [70]. The participation coefficient ranges from 0 to 1, where 1 indicated a node with many inter-modular connections. It is calculated for every node i as,

$$pc_i = 1 - \sum_{m \in M} \left(\frac{k_i(m)}{k_i}\right)$$
 (2.3)

where  $k_i$  is the degree of node *i*,  $k_i(m)$  is the total number of edges between node *i* and nodes in the module *m*, and *M* is the set comprising all the modules as defined in the community detection algorithm. In order to calculate the participation coefficient of a node, the community assignments, as detected by the Louvain algorithm, needs to be provided. Hence, the final measure that is considered is the average of the normalized participation coefficient calculated over all the iterations, as shown below,

$$PC_i = \sum_{iter \in total_{iter}} (pc_{i,iter})$$
(2.4)

where,  $pc_{i,iter}$  is the normalized participation coefficient (normalized across values of all nodes of each subject, range after normalization is 0-1) of node *i* calculated in iteration *iter*, and *total<sub>iter</sub>* is the total number of iterations of the community detection algorithm. This average,  $PC_i$ , is the final participation co-efficient considered.

#### **Mutual Information**

Mutual information is a common and reliable measure of dependence that, unlike correlation, captures both non-linear and linear relationships between the two variable X and Y. The mutual information, **MI**, is calculated as follows,

$$MI(X;Y) = D_{KL}(P_{(X,Y} \parallel P_X \otimes P_Y)$$
(2.5)

where, X and Y are the communities detected in the representative FCs of each age group. Representative FCs are calculated as the average FC matrix over all subjects in each age group. For our analysis, we used an open source implementation [73, 74, 75].

#### Modularity

Modularity is a measure of the extent of segregation and integration between different communities in a graph. Modular communities which have dense within-module connections and sparse betweenmodule connections, can be detected by various algorithms. These algorithms optimize the partitioning such that the detected communities in the graph have significantly denser intra-community edges and sparser inter-community edges when compared to a null model with the same edge distribution but randomly assigned edges. The quality of the partitioning can be quantified by a quality function also known as the modularity score, Q, that is calculated by equation 2.6 [76, 77, 78, 79, 80, 81].

$$Q = \frac{1}{2\mu} \sum_{ij} [A_{ij} - P_{ij}] \delta(c_i, c_j)$$

$$\mu = \frac{1}{2} \sum_{ij} A_{ij}$$
(2.6)

where  $A_{ij}$  is the adjacency graph with correlations between regions *i* and *j*  $P_{ij}$  is the correlation in the null model,  $c_i$  is the community assigned to node *i*, and  $\delta(c_i, c_j)$  is 1 if nodes *i* and *j* belong to the



Figure 2.1: The overview of the Louvain algorithm used for community detection and modularity calculation. Figure adapted from Figure 1 in Blondel et. al. (2008) [76].

same community, else it is 0. The Newman-Girvan model was considered as the null model [79]. In the current study, communities were detected using the Louvain algorithm [76] as implemented in the Brain Connectivity Toolbox [70]. Since the community detection algorithm is stochastic, the modularity score for each participant was calculated as the average over 1000 runs.

#### **Multilayer Modularity Maximization Algorithm**

Since the Louvain community detection is stochastic in nature, a generalized Louvain algorithm that maintains the homogeneity of the communities detected across different correlation matrices is used to detect communities while accounting for homogeneity [82]. Further, adjusting the scale and layer parameter account for the size of the detected community (finer vs coarser) and homogeneity maintained (nodes being treated as similar or dissimilar), respectively [83, 81]. The algorithm optimizes for the following modular-partition quality.

$$Q = \frac{1}{2\mu} \sum_{ijlr} \left( (A_{ijl} - \gamma_l P_{ijl}) \delta_{lr} + \delta(c_i, c_j) \omega_{jlr} \right) \delta(g_{il}, g_{jr})$$

$$\mu = \frac{1}{2} \sum_{ij} A_{ij}$$
(2.7)



Figure 2.2: An example of the multilayer community organization where the homogeneity of the nodes is maintained while changing communities across layers. Figure adapted from Figure 6 in Hanteer et. al. (2020) [84].

where i, j represent nodes and l, r represent different layers.  $A_{ijl}$  is the adjacency graph with correlations between regions i and j in layer l,  $P_{ijl}$  is the correlation in the null model in layer l,  $c_i$  is the community assigned to node i,  $\delta(c_i, c_j)$  is 1 if  $c_i = c_j$ , else it is 0,  $g_{il}$  is the community assignment of node i in layer l,  $\delta(g_{il}, g_{jr})$  is 1 if the community  $g_{il} = g_{jr}$ , else 0, and  $\delta l, r$  is 1 if l = r else 0. The scale and layer parameters were  $\gamma_l$  and  $\omega_{jlr}$ . The Newman-Girvan model was considered as the null model [79]. The adjacency matrix used as input is a supra-adjacency matrix with the layers as the diagonal entries. Each layer corresponds to a temporal window. The multi-layer and multi-scale parameter was selected based on the strategies mentioned in previous literature [81]. The multi-layer parameter was set to 1 hence the nodes are treated homogeneously across the layers. Since the modularity algorithm is stochastic in nature, we performed 1000 runs. The network metrics for each participant were calculated as the average over these 1000 runs.

#### Flexibility

Flexibility is a measure that captures the community reassignment dynamics across temporal windows at a nodal level [85]. The output of the multilayer maximization algorithm is a graph,  $G = N \times T$ , where N is the number of nodes and T is the number of layers (windows). Flexibility for node i is then calculated as,

$$F_i = \frac{m}{T-1} \tag{2.8}$$

where, m is the number of times the node has changed its community affiliation and T is the number of time steps (time windows). Nodes with high and low flexibility scores were computed as the top and bottom 33 percentile of all the flexibility scores. Further, we calculated the network-level flexibility scores by averaging the flexibility scores of individual nodes composing the large scale intrinsic predefined resting state networks [86]. High and low flexibility networks are calculated by averaging the flexibility scores of the constituent nodes showing high and low flexibility behaviour, respectively. Similarly, global flexibility was calculated as average over all the nodes per participant.

# 2.5 Statistical Analysis methods

#### ANOVA - One-Way

ANOVA (Analysis of Variance) is a statistical method used to compare the means of two or more groups. In a one-way ANOVA, we compare the means of a single dependent variable across different levels of a categorical independent variable. The p-value obtained from an ANOVA represents the probability of observing the obtained or more extreme difference in means between groups, assuming there is no true difference in the population means. A small p-value (typically below a significance level, e.g., p < 0.05) suggests evidence of a significant difference between at least one pair of group means [87].

#### **Pearson's Correlation**

Pearson's correlation coefficient is a statistical measure that quantifies the strength and direction of the linear relationship between two continuous variables. It ranges from -1 to +1, where -1 indicates a perfect negative linear relationship, +1 indicates a perfect positive linear relationship, and 0 indicates no linear relationship. A small p-value suggests that the observed correlation is unlikely to occur by chance alone, providing evidence for a significant linear relationship between the variables [88].

#### **Spearman's Correlation**

Spearman's correlation coefficient is a non-parametric measure that assesses the monotonic relationship between two variables. It is particularly useful when the relationship between variables is not strictly linear. Spearman's correlation coefficient ranges from -1 to +1, with -1 indicating a perfect negative monotonic relationship, +1 indicating a perfect positive monotonic relationship, and 0 indicating no monotonic relationship [89, 90].

# 2.6 Identifying important features - ML approach

Classifiers are used to predict the class of a given input based on a set of features. In this study, the classifiers were used to predict the age group of the subject based on their brain network features. The features used were the flexibility scores of different nodes in the brain network, which were hypothesized to be correlated with age. By training different classifiers on the features, the study aimed to identify

the most effective method for predicting age group and to identify which features were most important for accurate classification.

#### 2.6.1 Feature Selection and Reduction

Feature reduction and selection methods are used to reduce the dimensionality of the dataset by selecting a subset of relevant features. In this study, both unsupervised and supervised feature selection methods were used.

- **Principal Component Analysis (PCA)** is an unsupervised feature reduction method that can be used to analyze datasets with multicollinearity and categorical data. PCA extracts important information and stores it in "principal components". It seeks lines, planes, and hyperplanes in K-dimensional space that best approximate the data in terms of least squares. A line or plane that is the least squares approximation of a set of data points maximizes the variance of the coordinates on the line or plane. PCA is used to extract features that account for the most variation in the data [91, 92, 93].
- On the other hand, the **Maximum Relevance-Minimum Redundancy** (**MRMR**) algorithm is a supervised feature selection method that extracts nodes with maximum information but does not contain overlapping information, hence minimizing redundancy. MRMR selects features that have maximum relevance with the target variable and minimum redundancy with the already selected features. MRMR is a filter-based approach that ranks the features based on their relevance to the target variable and redundancy with the other features [74, 94, 95, 96].

In summary, PCA is an unsupervised feature reduction method that reduces the dimensionality of the data by selecting principal components that account for the most variation in the data. MRMR, on the other hand, is a supervised feature selection method that selects a subset of features with maximum relevance with the target variable and minimum redundancy with other features.

#### 2.6.2 Choice of classfier

Various classifiers were considered, with variants from linear to complex polynomial functions to describe the brain model and its functions best. The classifiers include support vector machines (SVMs) with linear and polynomial kernels, random forest classifiers, and logistic regression. These classifiers were chosen for their ability to handle high-dimensional data and capture non-linear relationships between variables.

SVMs are a popular classification algorithm that separates data points into different classes using a hyperplane. Linear SVMs assume that the data can be separated by a straight line or plane, while polynomial SVMs can capture non-linear relationships by mapping the data into a higher-dimensional space [97].

Random forest classifiers are an ensemble learning method that constructs multiple decision trees and combines their outputs to make a final prediction. This approach is useful for handling noisy or missing data and capturing complex variables' interactions. [98]

Logistic regression is a statistical technique that forecasts the likelihood of a binary result by analyzing one or more predictor variables. It is a simple and interpretable model that is often used as a baseline in classification tasks [99].

### 2.7 Regression analysis

In order to characterize the effect of age on the network measures and cognitive performance, a polynomial regression analysis was performed where the polynomial factor ranged from 1 to 10. Regression analysis is necessary to quantify, understand, and assess the relationship between one or more independent variables and a dependent variable. It allows for controlling confounding variables, examining nonlinear relationships, hypothesis testing, and predictive modelling, contributing to a comprehensive understanding of the impact of age on network measures and cognitive performance [100, 101]. Polynomial regression, specifically, extends the linear regression model by including polynomial terms of the predictor variables to capture nonlinear relationships.

The general equation for polynomial regression can be represented as

$$y = \beta_0 + \beta_1 x + \beta_2 x^2 + \ldots + \beta_n x^n + \varepsilon$$

where: y represents the dependent variable, x represents the predictor variable,  $\beta_0, \beta_1, \beta_2, \ldots, \beta_n$ are the coefficients corresponding to the polynomial terms, n represents the highest degree of the polynomial, and  $\varepsilon$  represents the error term.

When fitting the linear model with polynomial terms ranging from 1 to 10, polynomial regression models of increasing degrees were considered. Each additional degree allowed for more flexibility in capturing nonlinear relationships between the predictor and the dependent variable. Since higher degrees may capture more intricate patterns in the data but can also lead to overfitting, we used the metrics mentioned in the next section along with the Occam's razor principle [100, 102].

#### Metrics for the choice of regression model

When comparing regression models, we used AIC, MSE (Mean Squared Error), and R-squared (R2) which are commonly used metrics. Each metric provides different insights into the performance of the models.

AIC (Akaike Information Criterion): The AIC is a measure of model fit that takes into account the goodness of fit and the complexity of the model [103, 104]. It balances the trade-off between model fit

and model complexity. A lower AIC indicates a better model fit. AIC is often used for model selection and can be calculated using the formula

 $AIC = -2\ln(L) + 2k,$ 

where L is the maximum likelihood estimate of the model's likelihood function, and k is the number of parameters in the model.

The model with the lowest AIC is generally preferred as it indicates a good balance between fit and complexity.

MSE (Mean Squared Error): MSE measures the average squared difference between the predicted and actual values in the data [104, 105]. It can be calculated using the formula

$$MSE = \frac{1}{n} \sum_{i=1}^{n} (y_i - \hat{y}_i)^2,$$

where n is the number of observations, y represents the actual values, and  $\hat{y}$  represents the predicted values.

It quantifies the overall accuracy of the model predictions. A lower MSE indicates better prediction accuracy, as it reflects smaller errors between the predicted and observed values. MSE is widely used to evaluate the predictive performance of regression models.

**R2** (**R-squared**): R-squared represents the proportion of the variance in the dependent variable that is explained by the independent variables in the model [105]. It is calculated by the formula

$$R^2 = 1 - \frac{SS_{\text{res}}}{SS_{\text{tot}}},$$

where  $SS_{res}$  is the sum of squared residuals and  $SS_{tot}$  is the total sum of squares.

It measures the goodness of fit and indicates how well the model captures the variability in the data. R2 ranges from 0 to 1, with a higher value indicating a better fit. However, R2 can be misleading if used as the sole criterion for model comparison, as it increases with the addition of more variables.

To summarize, AIC focuses on model selection and trade-offs between fit and complexity, while MSE and R2 assess model prediction accuracy and goodness of fit, respectively. Further, in the cases 2 models has similar AIC, MSE and R2 scores, the simpler model was chosen according to Occam's razor.

In conclusion, this chapter provides an in-depth examination of the methodologies commonly employed in the current literature. These methodologies are carefully considered and deliberately chosen based on the specific requirements and objectives of the research. The CAMCAN dataset is used to conduct the analysis, which has proven to be a valuable resource in neuroscience studies. This dataset offers a rich and diverse collection of brain imaging data, allowing us to investigate various aspects of brain connectivity. A range of network measures is employed to evaluate the connectivity patterns within the brain. These measures enable us to quantify and analyze the intricate network properties and relationships among different brain regions. By utilizing these network measures, valuable insights can be gained into the complex organization of the brain's functional connectivity. Furthermore, various machine-learning techniques were leveraged to develop predictive and classification models. These techniques allow us to uncover patterns and relationships within the data and make predictions or classify different brain states or conditions. By applying these ML techniques, we aim to enhance our understanding of the brain's functioning and potentially contribute to diagnostic or prognostic applications.

# Chapter 3

# **Related Work**

In this chapter, a comprehensive survey of the existing literature concerning age-related transformations in brain structure, function, and cognition is presented. It explores a wide range of research endeavours aimed at understanding the modifications that manifest in the ageing brain. The chapter encompasses investigations examining structural modifications, such as the reduction in volume observed in specific brain regions and the decline in white matter integrity. Furthermore, it delves into functional modifications by highlighting alterations in neural activation patterns and connectivity networks identified in older individuals. The chapter also investigates cognitive alterations associated with the ageing process, encompassing declines in processing speed, memory function, and executive functions. In addition to reviewing empirical findings, the chapter discusses various theories proposed to explain these changes with age. It provides insights into theoretical frameworks that attempt to elucidate the underlying mechanisms of age-related brain alterations.

Gray matter and white matter are integral components of the central nervous system that work together to facilitate brain function. Gray matter, found predominantly in the cerebral cortex, is responsible for processing information, integrating sensory inputs, and supporting cognitive functions. It contains the cell bodies, dendrites, and synapses of neurons, forming the computational core of the brain. On the other hand, white matter consists of myelinated axons that establish connections between different regions of gray matter. As the brain's communication infrastructure, white matter enables the efficient transmission of electrical signals between brain regions. The myelin sheath surrounding white matter axons enhances signal conduction speed and facilitates information integration across neural networks. The collaborative interaction between gray matter and white matter is crucial for complex cognitive tasks, effective communication, and the regulation of bodily functions [106, 107].

### **3.1** Structural changes with age

Various measures can be used to assess the structural integrity of the brain, including volumetric changes, cortical thickness, and white matter integrity. Here are some of the observed changes in gray and white matter:

#### White matter

- White Matter Volume Reduction: ageing is associated with a gradual decline in white matter volume, particularly in frontal areas of the brain. This reduction may be attributed to decreased myelination, loss of axons, and changes in the density and organization of white matter fibers [6, 108, 109]. White matter volume is generally reduced in frontal areas of the ageing brain [110, 6, 111, 7, 112].
- White Matter Hyperintensities: White matter hyperintensities (WMHs) are areas of increased signal intensity observed in brain imaging, such as T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI. WMHs are commonly found in older individuals and are associated with small vessel disease, chronic ischemia, and damage to white matter tracts. They can disrupt the structural integrity of white matter and contribute to cognitive decline [113]. The frontal and occipital regions contributed to the highest to the affected tissues observed in older ages [5].
- White Matter Microstructural Changes: Diffusion tensor imaging (DTI) allows the assessment of white matter microstructure. With ageing, DTI studies have shown decreases in fractional anisotropy (FA) and increases in mean diffusivity (MD) in white matter tracts. These changes suggest alterations in white matter integrity, including reduced myelination, axonal degeneration, and changes in fiber density and orientation [114]. Anterior regions of the brain have been shown to exhibit the most significant structural deficiency in terms of white matter tracts [115].

#### Gray matter changes

- Gray Matter Volume Reduction: ageing is associated with a gradual decline in gray matter volume, particularly in regions involved in higher cognitive functions, such as the frontal and parietal cortices, as well as the insula and hippocampus [110, 6, 111, 7]. This reduction is thought to reflect neuronal loss, synaptic pruning, and reductions in dendritic arborization.
- Cortical Thinning: Age-related cortical thinning is observed in various brain regions, including the prefrontal and posterior cortices. While most studies show relatively stable cortical thickness in the visual cortex, the calcarine cortex, located near the primary visual cortex, has been found to display age-related atrophy [4, 110]. This thinning may be related to neuronal atrophy, reductions in synaptic connections, and changes in dendritic morphology.

#### Connectome

The brain's structural organisation can be represented as a graph, often called the connectome, where the edges correspond to white matter tracts connecting different brain regions. The thickness of these tracts determines the weight of the edges in the graph. Certain brain regions, such as the superior-frontal cortex, orbitofrontal cortex, anterior cingulate, lateral occipital cortex, and medial cortex, are less flexible and less susceptible to age-related changes. These regions are part of modules that span both hemispheres. It is important to note that the ageing process involves a shrinking corpus callosum, which leads to a decline in interhemispheric connections and affects the number of modules spanning across hemispheres [116]. On the other hand, brain regions with high nodal flexibility undergo significant changes over time. These regions include the temporal regions, motor and sensory areas, parietal lobe, and posterior cingulate. The participation coefficients of these regions show positive correlations with age, indicating increased integration within the network during ageing. Conversely, the parietal cortex becomes less integrated with age, as reflected by its negative correlation with the participation coefficient. These findings help explain bilateral activations in the parietal regions and changes in the posterior cingulate cortex observed in ageing [117].

Previous research has suggested that changes in frontal-striatal circuits are associated with declines in memory and executive function [12]. Differences in diffusion tensor imaging (DTI) measures of the anterior white matter have been observed between older adults with declining memory performance and those with intact memory functions. Additionally, the lateral occipital cortex exhibits low flexibility and participation coefficient values unrelated to age [8]. When examined at a global scale, the connectome reveals a complex network. The brain tends to cluster regions that require simultaneous activation while maintaining efficient information flow through dynamically changing "hubs" [13, 118]. This reflects a balance between optimizing information flow efficiency and minimizing wiring costs. The structural brain network exhibits characteristics of both segregation and integration, indicative of a modular organization [70]. The modularity of younger and older age groups tends to be higher than that of middle-aged groups [9]. Modularity calculation considers the number of uncovered clusters and the weights of connections (white matter tract thickness) between regions. During development, the brain exhibits more clusters with substantial integration among them, leading to high modularity. In adulthood, the brain becomes more segregated into functionally distinct, efficiently integrated clusters. In old age, structural deterioration leads to stronger within-module connections, resulting in higher modularity due to frequently traversed pathways [9].

### **3.2** Functional changes with age

The previous chapter discussed various approaches to capture the functional activity of the brain. Among them, functional magnetic resonance imaging (fMRI) is a commonly used and reliable method. It captures the signals related to changes in blood oxygen levels in different brain regions, known as the Blood-Oxygen-Level-Dependent (BOLD) signals. As the flow of oxygenated blood is influenced by the underlying structural connections formed by white matter tracts, the functional brain revealed through fMRI is expected to exhibit similarities to the connectome [119]. Connectivity analysis is a powerful tool to study age-related changes. It involves examining the functional connectivity between different brain regions or networks. This can be done using various methods, such as seed-based correlation analysis, independent component analysis (ICA), or graph theory-based network analysis [50, 120, 70]. Agerelated changes in connectivity strength, network topology, or network efficiency can provide insights into functional brain changes with ageing. A few key findings related to the changes in connectivity analysis:

- 1. **Decreased intra-network connectivity:** Several studies have shown a decline in functional connectivity within specific networks such as the DMN, executive control network (ECN), and sensorimotor network (SMN) with increasing age. This decrease in intra-network connectivity suggests a loss of integration and coordination within these networks [121].
- 2. **Increased inter-network connectivity:** On the other hand, there is evidence of increased functional connectivity between different networks. Older adults tend to exhibit greater coupling between the DMN and ECN, suggesting a compensatory mechanism to maintain cognitive performance [122].
- 3. Altered network dynamics: Age-related changes in connectivity analysis also include alterations in network dynamics. Older adults may show reduced flexibility and adaptability of brain networks, leading to a more rigid and less adaptive functional connectivity profile [121, 122, 123].
- 4. **Regional-specific connectivity changes:** Specific brain regions may exhibit age-related changes in connectivity. For example, frontal regions often show increased connectivity with other brain regions, which may indicate compensatory mechanisms [124, 125].

Specifically, the changes in functional networks associated with ageing can be summarized as follows:

- 1. Decreased Default Mode Network (DMN) Connectivity: ageing is associated with reduced functional connectivity within the DMN, a network of brain regions involved in self-referential thinking and mind-wandering. This decline in DMN connectivity may contribute to age-related cognitive decline and disrupted introspective processes [126, 127, 121].
- 2. **Increased Frontal Activation**: Older adults often exhibit increased activation in frontal brain regions during cognitive tasks. This frontal overactivation may reflect compensatory mechanisms to maintain cognitive performance despite age-related changes in other brain regions [128, 112, 121].
- 3. **Reduced Ventral Visual and Sensory Activation**: There is growing evidence that ageing is associated with decreased neural specificity and activation in ventral visual and sensory cortex. Despite the preserved volume, older adults show diminished activation and less neural specificity in regions such as the fusiform face area, parahippocampal place area, and lateral occipital area, which are specialized for face recognition, object categorization, and letter processing compared to young adults. These regions are [11, 129, 130, 125, 131].


Figure 3.1: Surface plots of RSNs - Functional Networks uncovered in the resting-state brain. A, Default mode network. B, Somatomotor network. C, Visual network. D, Language network. E, Dorsal attention network. F, ventral attention network. G, Frontoparietal control network. Figure adapted from Lee et al. (2013) [50].

- 4. Altered Salience Network Function: The salience network, involved in detecting and switching attention, undergoes functional changes with age. Older adults may exhibit increased salience network activation during task performance, potentially reflecting compensatory efforts to maintain attentional control and task performance [132].
- 5. Impaired Fronto-Parietal Network Function: The frontoparietal network, responsible for executive functions, shows altered activation patterns in older adults. Age-related decline in this network's function may contribute to deficits in working memory, cognitive control, and attentional processes. An illustrative example is observed in the hippocampal and parahippocampal regions, where volumetric shrinkage is typically associated with dementia. However, studies in the literature suggest that compensatory mechanisms, such as bilateral frontal overactivation, initially attempt to offset the decline in hippocampal activation. However, ver time, these compensatory mechanisms may reach a pathological limit, beyond which the trade-off between compensation and functional decline is no longer effective. [12, 133, 11, 14, 134, 15, 135, 136].

# **3.3** Behavioural and cognitive changes with age

As individuals age, cognitive abilities tend to undergo changes that can vary across different domains. While some cognitive functions may decline, others may remain stable or even show improvements. Here are some specific changes observed in brain cognition with age:

- 1. **Processing Speed:** One of the most consistent changes observed is a decline in processing speed, which refers to the ability to quickly perceive and respond to information. This decline is attributed to various factors, including changes in neural processing, reduced efficiency in information transmission, and alterations in brain connectivity. [23, 10, 24, 25]
- Working Memory: Working memory involves the temporary storage and manipulation of information. While some aspects of working memory may decline with age, such as the ability to maintain multiple items simultaneously, other aspects, like the ability to use strategies or chunk information, may remain relatively stable [26].
- 3. **Episodic Memory:** Episodic memory refers to the ability to recall specific events from the past. This ability tends to decline with age, particularly in tasks involving free recall. However, older adults can often compensate for episodic memory decline through the use of memory strategies or by relying on semantic memory [27].
- 4. **Semantic Memory:** Semantic memory encompasses general knowledge about the world, including facts, concepts, and vocabulary. This type of memory tends to remain relatively stable or even improve with age, as it is based on accumulated knowledge and experiences [28].

However, factors such as education, lifestyle, and genetics can influence the trajectory of cognitive change in older adults.

To identify and understand the aspects of cognition mentioned earlier, various assessment methods and tests can be employed. These assessments are designed to measure different cognitive functions and provide insights into an individual's cognitive abilities. Here are a few commonly used methods:

**Neuropsychological Tests:** These tests assess different cognitive domains such as processing speed, working memory, attention, and episodic memory. Examples include the Trail Making Test, Digit Span Test, Stroop Test, and the Rey Auditory Verbal Learning Test. These tests typically involve tasks that measure specific cognitive processes and provide quantitative measures of performance [137, 138].

**Cognitive Screening Tools:** Screening tools like the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are brief assessments that provide a snapshot of overall cognitive functioning. These tools cover multiple cognitive domains and are useful for initial screening or identifying potential cognitive impairments [138].

**Longitudinal Studies:** Longitudinal studies track individuals over an extended period, often years, and repeatedly measure their cognitive abilities. By examining changes in cognitive performance over time, these studies provide valuable insights into the ageing process and the trajectory of cognitive decline or stability [133, 56].

Regarding intelligence, two key concepts are often discussed in relation to cognition: crystallized intelligence and fluid intelligence.

- Fluid Intelligence: Fluid intelligence refers to the capacity to think logically, solve novel problems, and adapt to new situations. It involves the ability to reason, identify patterns, and draw inferences without relying heavily on prior knowledge or experience. Fluid intelligence is considered to be independent of specific knowledge domainqs and is often associated with cognitive processes such as working memory, abstract reasoning, and mental flexibility. It tends to peak in early adulthood and gradually declines with age.
- **Crystallized Intelligence:** Crystallized intelligence, on the other hand, refers to the accumulation of knowledge, skills, and information acquired through experience and education. It involves the application of previously acquired knowledge, language proficiency, and domain-specific expertise. Crystallized intelligence is closely related to long-term memory and is influenced by cultural and educational factors. It tends to increase throughout adulthood as individuals gain more knowledge and experience.

Two commonly used tasks to characterize these two different aspects Benton's face recognition task and Cattell's puzzle task.

# **3.4** Theories of ageing

People generally function remarkably well even into advanced old age, and do so even in the presence of a great deal of pathology as discovered at autopsy (T. W. Mitchell et al. 2002).



Figure 3.2: Figure depicting the changes in various cognitive aspects throughout lifespan. Accrued knowledge, like vocabulary, is resilient to ageing while cognitive processing, long-term memory and working memory show a decline with ageing. Figure adapted from Park et al. (2002)[139].

The puzzle for cognitive neuroscientists is not so much in explaining age-related decline, but rather in understanding the high level of cognitive success that can be maintained by older adults in the face of such significant neurobiological change

[10]. Various theories of ageing have been proposed to account for the maintenance of cognitive performance inspite of a visible decline in the structural architecture.

## **Compensation and Dedifferentiation**

In the ageing human brain, overactivation, characterized by a relative increase in activation compared to younger individuals, is a common phenomenon observed in various brain regions. This overactivation is believed to reflect a compensatory mechanism aimed at maintaining cognitive performance in older individuals. Additionally, the dedifferentiation theory proposes that with age, there is an increase in functional similarity across brain regions, resulting in a diminished distinctiveness of neural responses[16, 20, 11, 140, 141].

## **Posterior-Anterior Shift in ageing - PASA**

The PASA (posterior-anterior shift with age) theory posits that there is a decline in activation in occipitotemporal regions and a corresponding increase in activation in frontal regions among older individuals. This theory suggests a shift in neural activity patterns with age, with a decrease in occipital activity and an increase in prefrontal activity. The HAROLD (hemispheric asymmetry reduction in older adults) theory provides a more detailed explanation for the increased prefrontal activation in older adults [15, 142]. Furthermore, older adults exhibit reduced occipital activity but enhanced prefrontal activity, which is positively associated with cognitive performance and negatively correlated with occipital activity [15, 17]. This pattern of brain activation aligns with the CRUNCH (compensation-related utilization of neural circuits hypothesis) theory [143]. The PASA pattern is considered to be a genuine ageing phenomenon and supports the compensation account, which suggests that increased prefrontal activation compensates for deficits in occipital regions [15]. However, while the PASA theory offers an alternative perspective on age-related brain activation changes, its limitations include oversimplification, lack of specificity, limited explanatory power, and inconsistencies in empirical findings.

## Hemispheric Asymmetry Reduction in Older Adults - HAROLD

The HAROLD theory suggests that compensatory or dedifferentiation processes reduce hemispheric asymmetry in the prefrontal cortex among older individuals compared to younger individuals. This theory explains the increased symmetry of activation observed across hemispheres in older adults. Specifically, older adults exhibit additional activation in the opposite hemisphere, particularly in the prefrontal cortex, compared to younger adults [128]. While HAROLD theory provides valuable insights, it does not fully account for all aspects of age-related changes in brain activation patterns.

One limitation is that the theory focuses primarily on the prefrontal cortex and does not consider other brain regions or cognitive functions. Additionally, some studies have found mixed results and inconsistencies in hemispheric activation patterns among older adults, suggesting that the theory may not apply universally [144]. Furthermore, the HAROLD theory does not explain the underlying mechanisms driving compensatory or dedifferentiation processes in older individuals. It does not address the specific factors or neural processes that lead to the observed changes in activation patterns. Overall, the HAROLD theory partially explains age-related changes in hemispheric activation.

## **Compensation-Related Utilization of Neural Circuits Hypothesis - CRUNCH**

The CRUNCH (compensation-related utilization of neural circuits hypothesis) theory proposes an explanation for the observed overactivation in the ageing brain, suggesting that it is primarily a compensatory mechanism. This theory argues that the overactivation seen in regions of the ageing brain is not a result of disease or a significant deviation from what is expected, as these regions also show activation in the young brain. According to the theory, when the task demand is low, the overactivation observed in specific regions of the older age group is primarily compensatory. This is supported by the fact that the performance levels between the young and old age groups remain similar under these conditions [145]. However, beyond a certain level of task demand, the older age groups experience a decline in performance. This decline is attributed to a lack of available resources for activation, indicating that the brain reaches a "resource ceiling" in older age that hampers further activation of regions.

The compensation-related utilization of neural circuits hypothesis focuses on the trade-off between the resources available for recruitment and cognitive performance. It suggests that in older age, the brain reaches a "resource ceiling" that hinders further activation of regions, leading to a decline in performance [145].

While the CRUNCH theory provides valuable insights, it may not fully address certain aspects related to the mechanisms underlying resource limitations and the extent to which they contribute to performance decline in older adults.

## Scaffolding theory of ageing and Cognition - STAC

The STAC theory, which stands for Scaffolding Theory of ageing and Cognition, presents a framework to explain cognitive performance in ageing. According to this theory, scaffolding serves as a secondary circuitry, similar to what is observed in the early stages of skill learning, by forming new connections, strengthening relevant existing connections, and pruning redundant pathways [10]. It is a lifelong process, not limited to older ages alone. Certain brain regions that experience age-related decline, such as the hippocampus and ventral visual cortex, may recruit resources from the prefrontal cortex as part of the scaffolding mechanism. Scaffolding networks are typically activated in response to challenges, whether extrinsic (such as higher task demands) or intrinsic (such as transient effects like lack of sleep or more permanent ones like ageing).

Although scaffolded networks are less efficient, relying solely on declining honed networks in old age would lead to poorer performance. Like the CRUNCH theory, as the brain ages, the need for scaffolding becomes greater than the extent of reorganization and plasticity. Additionally, pathology disrupts the reparative process due to cellular health decline, which limits the ability of regions to engage in scaffolding. This, combined with the unique challenges introduced by diseases, eventually results in a collapse of the secondary compensatory network. Factors that promote scaffolding include genetic susceptibility to ageing, higher levels of physical fitness, cognitive stimulation, and other activities that enhance neurotrophic factors and serotonin [10, 143]. However, its limitations include the lack of mechanistic specificity, variability in scaffolding effects, limited consideration of other factors, generalizability, and reliance on cross-sectional evidence.

# 3.5 Challenges in current methodologies

The challenges faced in the field of ageing neuroscience include methodological variability, complex interplay of factors, heterogeneity of ageing, and the need for longitudinal studies. To elaborate further, the following are some major challenges faced.

- Methodological variability: There is a lack of standardization in the methods used to study ageing and the brain. Different studies employ different techniques, measures, and study designs, making it challenging to compare findings across studies and establish consistent conclusions [29, 30].
- Complex interplay of factors: ageing is a multifaceted process influenced by various factors, including genetic, environmental, lifestyle, and social factors. Untangling the complex interactions

and understanding the relative contributions of these factors to age-related changes in the brain poses a significant challenge [10].

- Heterogeneity of ageing and individual differences: ageing is a highly heterogeneous process, with considerable individual differences in cognitive abilities, brain structure, and function. This heterogeneity poses challenges for generalizing findings across older adults and understanding the underlying mechanisms [123, 146]
- Lack of longitudinal studies: Many studies in ageing neuroscience are cross-sectional, providing only snapshots of brain changes at specific time points. Longitudinal studies that track individuals over time are necessary to understand the trajectory of brain changes and establish causal relationships [33].

To summarize, the chapter presents a comprehensive synthesis of the literature on age-related changes in brain structure, function, and cognition, offering insights into the various theories proposed to explain these changes. It underscores the importance of interdisciplinary research in unraveling the intricate processes underlying brain ageing and highlights the need for further investigations to deepen our understanding of the ageing brain and its implications for cognitive function. In the next chapter, we aim to bridge the gap between the two types of measures - static and dynamic and intuitively understand the differences in the functional organization in young and old age groups. We use machine learning in addition to graph network analysis to identify networks and regions that characterize healthy ageing.

# Chapter 4

# Characterizing the Dynamic Reorganization in Healthy Ageing -Young vs Old $^1$

In the previous chapter, we saw how the brain networks undergo various topological and functional alterations during healthy ageing. Previous studies have shown that the dedifferentiation of the functional modules could be one of the hallmarks of large-scale brain networks and alterations through the lifespan. This modular organization and alterations may be critically linked to a variety of neurodegenerative disorders and cognitive deficits encountered during ageing. In spite of accumulating evidence based on tracking static functional connectivity (FC) and modularity in characterizing dedifferentiation associated with ageing, there is a gap in understanding the brain dynamics of modular segregation and integration through the lifespan. Using the Cam-CAN dataset (young: 18-44, mean 32 years, old: 65-88, mean 75 years), we characterize the modular reorganization using dynamic measures like flexibility, to find characteristic nodes that make up the stable core and flexible periphery in the young and old age groups. In this chapter, we hypothesize that the nodes that exhibit higher flexibility in the older age groups will be negatively correlated with modularity since these nodes 'compensate' for the functional integration while ensuring that the segregation is efficient. Our results demonstrate that the regions from the Default Mode network (DMN) show a negative correlation with modularity in the old age groups. Further, nodes from Limbic, SensoriMotor (SMN) and Salience networks show a positive correlation with modularity. These networks that are responsible for higher-order cognitive functions, e.g., decision making, attentional control, cognitive flexibility, are found to make up a stable core as evidenced by their low flexibility scores. We also trained various classifiers using node flexibility scores as features for the binary (young vs old) classification task. Support Vector Machine (SVM) with Gaussian kernel trained on a reduced-dimensional feature set gave the best classification results. The features (nodes) that are found to be important for classification concur with those identified through the data-driven network measures based analysis.

<sup>&</sup>lt;sup>1</sup>As published in 2022 International Joint Conference on Neural Networks (IJCNN) [147]

# 4.1 Introduction

The human brain is dynamic and undergoes changes throughout the lifespan. New connections are formed between anatomical regions, frequently used pathways are strengthened and old, scarcely used pathways are forgotten [148]. The connections between regions usually form clusters called modules / communities [149]. Biologically, the connections between regions tend to minimize the wiring costs – hence as one moves from early ages (7-18) to young- middle ages (19-60), there are fewer long range connections and more short range connections [18, 150, 151]. This is evidence of a modular behaviour in the developed brain where there is structural segregation into modules with high within-module connections and few integrative links that are responsible for the information flow between modules [80]. In contrast, in the older ages (> 60), there is an onset of structural decline, hence there are fewer short range connections as well. However, the cognitive performance continues to stay stable. Many theories have tried to explain the behaviour of the functional brain that upholds healthy and normal cognition [148, 20, 140].

Representing the brain connections as a network can give us insight into the whole-brain organization through a data-driven analysis of the network. Graph theory and related measures like modularity are often used to characterize the organization of the brain on multiple scales (nodal, meso-scale and global/whole-brain) [61, 152, 148, 153].

Modularity has been shown to follow a U-shaped trend as a function of age, in the sense that the trend of modularity is higher in the younger and older brains as compared to that of the middle age [18, 150]. Further, individuals who have higher modularity have also shown to perform better in lower-order cognitive tasks while individuals who have a lower modularity have shown to perform better in higher order cognitive tasks [154, 155]. Flexibility, a node-level measure which captures the dynamic changes in the community assignments across time windows, has also similarly been shown to be relate with cognitive performance. Higher flexibility has been observed in individuals who can perform better in higher order cognitive tasks [156, 157]. It has also been used as a biomarker to characterize diseases like autism [158, 21, 159]

Work done to characterize network topology have mainly considered static measures and dynamic measures individually. There has not been much literature that compares static (modularity) and dynamic (flexibility) measures of the topological reorganization together to characterize healthy ageing [158, 160]. Here, we compare modularity and flexibility which are both measures of network reorganization. In this study, we hypothesize that the networks that exhibit lower flexibility in the older age groups will be positively correlated with modularity since these nodes maintain a stable core as measured by modularity. Networks that exhibit higher flexibility should be negatively correlated with modularity since they make up the peripheral regions of the dynamic core that uphold integration of information and higher level functions [161]. We observed an overlap of features identified through classification models with data-driven methods.

# 4.2 Materials and Methods

## 4.2.1 Participants

The data was collected as part of stage 2 of the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) project (available at http://www.mrc-cbu.cam.ac.uk/datasets/camcan)[52]. The Cam-CAN datset is a large-scale multimodal, cross-sectional study. The database includes raw and pre-processed structural magnetic resonance imaging (MRI), resting state and tasks-based activations using functional MRI (fMRI) and Magnetoencephalogram (MEG), behavioural scores, demographic and neuropsychological data. Stage 1 consisted of 3000 participants of which a subset of approximately 700 participants were selected. The selection criteria was based on cognitively health (MMSE score > 25), no past or current treatment for drug abuse or usage. The study was in compliance with the Helsinki Declaration. It was approved by the Cambridgeshire 2 Research Ethics Committee. The participants were grouped into young and old age groups (young: 18-44, mean 32 years, 200 participants, old: 65-88, mean 75 years, 223 participants).

# 4.2.2 Data acquisition and preprocessing

The fMRI data was collected at Medical Research Council Cognition and Brain Sciences Unit, on a 3T Siemens TIM Trio scanner with a 32-channel head coil. The eyes-closed resting state fMRI data was acquired using Echo-Planar Imaging (EPI) sequence. The following were the parameters: TR = 1970 ms, TE = 30 ms; voxel size =  $3.0 \times 3.0 \times 3.7$  mm; flip angle =  $78^{\circ}$ ; acquisition time = 8 min 40 s, total number of volumes = 261; 32 axial slices per volume (slice thickness 3.7mm, interslice gap of 20%) acquired in descending order.

Pre-processed data was provided by Cam-CAN research consortium. Anatomical Automatic Labelling atlas (AAL) (toolbox available at http://www.gin.cnrs.fr/tools/aal) was used for parcellating the brain into 116 regions whose mean BOLD timeseries signals were calculated [53].

## 4.2.3 Modeling the functional connectivity

The brain can be represented as a graph where the regions of interest (ROIs) constitute nodes and the edges represent the similarity of the BOLD activation between the nodes. In this study, we used Pearson's correlation to measure the strength of functional connectivity between regions.

#### 4.2.3.1 Static Functional Connectivity

A straightforward and effective way to represent the functional coupling of the nodes (ROIs) is to consider the average Pearson's correlation of the fluctuations of the BOLD signal across the scan time. This method allows us to observe the meso-scale architecture of the steady state brain organization pattern averaged over a long period of time(scan time).

#### 4.2.3.2 Dynamic Functional Connectivity

While the static FC gives us insight into the architecture of the networks that remain stable over time, the non-trivial dynamics are hidden [63, 64]. In the dynamic functional connectivity (dFC) analysis in this paper, we used a tapered sliding window approach and represented the entire time-series in windows of 44 seconds based on the strategies followed in [68, 69].

# 4.2.4 Network measures

#### 4.2.4.1 Modularity

Modularity is a measure of the extent of segregation and integration between different communities in a graph. Modular communities which have dense within-module connections and sparse betweenmodule connections, can be detected by various algorithms. These algorithms optimize the partitioning such that the detected communities in the graph have significantly denser intra-community edges and sparser inter-community edges when compared to a null model with the same edge distribution but randomly assigned edges. The quality of the partitioning can be quantified by a quality function also known as the modularity score, Q, that is calculated by equation 4.1 [76, 77, 78, 79, 80, 81].

$$Q = \frac{1}{2\mu} \sum_{ij} [A_{ij} - P_{ij}] \delta(c_i, c_j)$$

$$\mu = \frac{1}{2} \sum_{ij} A_{ij}$$
(4.1)

where  $A_{ij}$  is the adjacency graph with correlations between regions *i* and *j*  $P_{ij}$  is the correlation in the null model,  $c_i$  is the community assigned to node *i*, and  $\delta(c_i, c_j)$  is 1 if nodes *i* and *j* belong to the same community, else it is 0. The Newman-Girvan model was considered as the null model [79]. In the current study, communities were detected using the Louvain algorithm [76] as implemented in the Brain Connectivity Toolbox [70]. Since the community detection algorithm is stochastic, the modularity score for each participant was calculated as the average over 1000 runs.

## 4.2.4.2 Multilayer Modularity Maximization Algorithm

Since the Louvain community detection is stochastic in nature, a generalized Louvain algorithm that maintains the homogeneity of the communities detected across different correlation matrices is used to detect communities while accounting for homogeneity [82]. Further, adjusting the scale and layer parameter account for the size of the detected community (finer vs coarser) and homogeneity maintained (nodes being treated as similar or dissimilar), respectively [83, 81]. The algorithm optimizes for the

following modular-partition quality.

$$Q = \frac{1}{2\mu} \sum_{ijlr} \left( (A_{ijl} - \gamma_l P_{ijl}) \delta_{lr} + \delta(c_i, c_j) \omega_{jlr} \right) \delta(g_{il}, g_{jr})$$

$$\mu = \frac{1}{2} \sum_{ij} A_{ij}$$
(4.2)

where i, j represent nodes and l, r represent different layers.  $A_{ijl}$  is the adjacency graph with correlations between regions i and j in layer l,  $P_{ijl}$  is the correlation in the null model in layer l,  $c_i$  is the community assigned to node i,  $\delta(c_i, c_j)$  is 1 if  $c_i = c_j$ , else it is 0,  $g_{il}$  is the community assignment of node i in layer l,  $\delta(g_{il}, g_{jr})$  is 1 if the community  $g_{il} = g_{jr}$ , else 0, and  $\delta l, r$  is 1 if l = r else 0. The scale and layer parameters were  $\gamma_l$  and  $\omega_{jlr}$ . The Newman-Girvan model was considered as the null model [79]. The adjacency matrix used as input is a supra-adjacency matrix with the layers as the diagonal entries. Each layer corresponds to a temporal window. The multi-layer and multi-scale parameter was selected based on the strategies mentioned in previous literature [81]. The multi-layer parameter was set to 1 hence the nodes are treated homogeneously across the layers. Since the modularity algorithm is stochastic in nature, we performed 1000 runs. The network metrics for each participant were calculated as the average over these 1000 runs.

#### 4.2.4.3 Flexibility

Flexibility is a measure that captures the community reassignment dynamics across temporal windows at a nodal level [85]. The output of the multilayer maximization algorithm is a graph,  $G = N \times T$ , where N is the number of nodes and T is the number of layers (windows). Flexibility for node *i* is then calculated as,

$$F_i = \frac{m}{T - 1} \tag{4.3}$$

where, m is the number of times the node has changed its community affiliation and T is the number of time steps (time windows). Nodes with high and low flexibility scores were computed as the top and bottom 33 percentile of all the flexibility scores. Further, we calculated the network-level flexibility scores by averaging the flexibility scores of individual nodes composing the large scale intrinsic predefined resting state networks [86]. High and low flexibility networks are calculated by averaging the flexibility scores of the constituent nodes showing high and low flexibility behaviour respectively. Similarly, global flexibility was calculated as average over all the nodes per participant.

# 4.2.5 Statistical Analysis

#### 4.2.5.1 Age effects on flexibility

We retained nodes that showed flexibility changes across age for further analysis. This set of nodes were further considered for age related comparisons. Further, using a one-way ANOVA, the network-level flexibility scores were compared across age groups to check for statistically significant differences.

## 4.2.5.2 Modularity and flexibility relation

Static modularity uncovers communities that remain stable across the entire scan time. Using nonparametric correlation, the relation between modularity and flexibility was calculated. This was calculated for flexibility scores at a nodal, network-level and global scale.

# 4.2.6 Classification

We investigated learning supervised classification models based on the flexibility scores of nodes as features. Each feature vector represents the flexibility scores of all the participants for the corresponding node. The aim is to see if such classification models can perform classification of brain age based on the flexibility scores. Further, we explored distinctive features (nodes) that were identified by the machine learning model while classifying participants into old or young age group and compare the results with the insights from the data-driven, graph measures-based analysis described in the previous sections.

## 4.2.6.1 Feature Selection / Reduction

Two feature reduction/selection procedures were employed. Unsupervised feature reduction using principal component analysis (PCA) was used. A supervised feature selection using Maximum Relevance-Minimum Redundancy (MRMR) algorithm was also performed. PCA identified 17 features that accounted for 95% of the variance. The MRMR algorithm captures the best 'K' features that have maximum relevance with the target variable (here, the class label young vs old) while minimizing the redundancy with the other features [94, 95]. Classification was done by varying K from 10, 15 and to 20. Beyond 20, the predictor scores of the features calculated by the MRMR algorithm were very low, as shown in Figure 4.6. The highest classification accuracy was obtained with K = 20.

#### 4.2.6.2 Choice of classifier

Multiple classifiers were used to categorize participants into young and old age groups. SVMs, especially with non-linear kernel functions, have been shown to be efficient while classifying into different age groups with various features [162, 163, 164]. This is mainly due to SVMs' resilience to overfitting [165]. We used baseline models like Logistic Regression, Linear Discriminant Analysis, K-Nearest Neighbours, and Support Vector Machines (SVM) with linear, quadratic and Gaussian kernels. SVM with Gaussian kernel yielded the best performance.

# 4.3 **Results and Discussion**

## 4.3.1 Modularity and Age

Static modularity shows how modular a given functional graph is, i.e., how functionally segregated the graph is. It measures the whole-brain reorganization over a long time period. A higher network modularity is indicative of segregation used in lower order tasks while a lower modularity is indicative of a network-wide integration observed in higher order cognitive tasks [155, 154]. It was observed that there was a statistically significant increase in modularity in the older age groups as compared to the younger age groups, shown in Fig. 4.1. This is in line with previous literature [166].



Figure 4.1: Modularity scores of participants across age groups. The difference between the young and old age groups' scores shown here is statistically significant (p < 0.05). The mean modularity scores are indicated by the red line in the box plot while the outliers are indicated by the red '+' signs.

# 4.3.2 Modularity vs Global Flexibility

To represent the brain dynamics, different functional connectivity configurations can be considered as attractor states. Static modularity measures the depth of the attractor while flexibility measures the frequency of transitions between the states. Deeper states would hence be more stable, with reduced flexibility [167, 168, 161]. Following this intuition, flexibility is expected to show a negative correlation with modularity. This is observed since both the young and old age groups show a negative correlation with global flexibility [160]. A lower correlation score was observed in the older age group implying a stronger negative correlation between the two measures (Fig. 4.2). Higher correlation in the younger age group could be due to the high integration while maintaining high segregation [18, 150]. In the older age groups, the modularity remains high possibly because of the high connection weights instead of the



Figure 4.2: Correlation between static modularity and global flexibility in old and young age groups. The correlation in the old age group is lower than that in the younger age group, implying a stronger relation between modularity and global flexibility in the older age groups. Correlations for both age groups are statistically significant at p < 0.05

sheer number of connections. At the same time, due to dedifferentiation, the flexibility also is expected to remain high [148, 20, 140].

## 4.3.3 Modularity vs High/Low Node flexibility

Since a higher flexibility would mean more participation in multiple communities, static modularity and flexibility are expected to show a negative correlation in a stable network. High and low flexibility networks are averages of the top and bottom 33 percentile nodes (constituting the respective networks) based on flexibility scores respectively. In the older age groups, the Visual and Control networks comprised the nodes with high flexibility that showed a statistically significant negative correlation with modularity. Whereas, in the young and old age groups, the Limbic system showed a positive correlation with modularity when nodes of low and high flexibility scores were considered. This can be seen in Fig. 4.3 and Fig. 4.4.

## 4.3.4 Network-level changes across age

Network-wise flexibility was calculated to be the average flexibility of the nodes that constituted the intrinsic pre-defined resting-state network. When comparing the flexibility scores at the network level across young and old age groups, as shown in Fig. 4.5, Visual, SensoriMotor (SMN), and Salience-Ventral Attention (SalVentAttn) networks showed a statistically significant difference. The flexibility of these networks showed a positive correlation with modularity in both young and older age groups. This could be indicative of a high segregation while the number of integrative hubs are also high. Further, when correlated with modularity, the flexibility of Default Mode Network (DMN) showed a negative correlation with modularity in the older age groups. This indicates that the regions in DMN constituted a flexible periphery.



Figure 4.3: Distribution of high network flexibility scores. The network flexibility score was calculated as the average of the constituent nodes that showed high flexibility scores. There was a significant difference (p < 0.05) in the flexibility scores of Control and Visual network across age. Further, Control and Visual network showed a negative correlation with modularity (p < 0.05) in the old age groups, implying that a higher flexibility in these networks would observe a decrease in modularity. On the other hand, regions in the Limbic network with high flexibility showed a positive correlation with modularity (in both young and old age groups) (p < 0.05), implying that nodes belonging to the network contribute to an increase in modularity inspite of the increase in flexibility.



Figure 4.4: Distribution of low network flexibility scores. The network flexibility score was calculated as the average of the constituent nodes that showed low flexibility scores. Salience and Ventral Attention (SalValAttn), Visual, Control and Limbic networks all showed a significant difference in flexibility across age groups. In the old age group, Visual and Limbic networks showed a positive correlation with modularity (p < 0.05), implying that in the old age group these nodes observed a comparatively higher/lower flexibility value that contributes to an increase/decrease in the modularity . Nodes in the Control network showed a negative correlation (p < 0.05), where the older age groups observed a comparatively lower flexibility which would explain the higher modularity. On the other hand, all the networks showed a positive correlation with modularity in younger age groups (p < 0.05), implying that an increase/decrease in the flexibility values of the constituent nodes would reflext in the higher/lower modularity values.



Figure 4.5: Network-level flexibility comparison across age groups. The SensoriMotor (SMN), Salience and Attention (Ventral) networks show a significant reduction in the old age group. The star (\*) indicates a significant difference (at p < 0.05) in network flexibility across the age groups. The arrow indicates a statistically significant correlation of the network with age, and the direction (up/down) indicates the nature of the correlation (positive/negative), respectively.

# 4.3.5 Classification

In the current study, features extracted from the network measure 'flexibility' are considered. The features selected for classification were selected based on the supervised MRMR algorithm. The features that showed the highest 20 predictor scores were selected (Fig. 4.6. Among the classifiers, Support Vector Machines (SVM) using a Gaussian kernel of scale 3.5 outperformed the other classifiers, as shown in Table 4.1. This further strengthens the efficiency of SVMs as classifiers used in the neuroimaging context [169, 164, 163]. The comparison across different SVM kernel functions and features used in literature is shown in Table 4.2.

#### **4.3.6** Overlap with Network Statistics

The important features detected had a lot of similarities with the characteristic nodes uncovered in network statistics. Regions that showed high importance from both machine learning models and network based statistics were primarily from cuneus, parahippocampal, insula, inferior frontal regions and, posterior and anterior cingulum. More details can be found in Table. 4.3.



Figure 4.6: The predictor ranks vs predictor scores as calculated by the MRMR algorithm. The x-axis shows the predictors (nodes/ROIs) sorted by their ranks indicating the 'K' best features and the y-axis denotes the predictor score as calculated by the supervised MRMR algorithm [94, 95]. The highest classification score was obtained with K=20.

# 4.4 Conclusion

One of the enduring puzzles in cognitive neuroscience is how brain maintains functional stability in the face of structural decline in the old age. Several attempts have been made at addressing the puzzle from various perspectives – data-driven analysis using statistical and graph-theoretic measures as well as whole brain computational models. In this paper, we attempted to address the gap in understanding the brain dynamics of modular segregation and integration through the lifespan. We used Cam-CAN dataset investigating ageing related changes from the structural and functional data acquired from participants with ages ranging from 18 to 88 years. We characterized the modular reorganization using dynamic measures such as flexibility in order to identify characteristic nodes that make up the stable core and flexible periphery in the young and old age groups.

The analysis of the graph theoretic measures demonstrate that nodes that exhibit higher flexibility in the older age group are negatively correlated with modularity and it seems that these nodes are compensating for the functional integration while ensuring that the segregation is efficient. The regions that exhibited negative correlation with modularity are from the Default Mode network (DMN) in the old age groups. Regions from Limbic, SensoriMotor (SMN) and Salience networks show a positive correlation with modularity. It is interesting to note that the identified regions and the corresponding networks are related to higher-order cognitive functions such as decision making, attentional control, and cognitive flexibility and these are found to make up a stable core as evidenced by their low flexibility scores.

To complement this data-driven analysis using graph theoretic measures and in order to find independent evidence for the relevance of the regions identified, we constructed machine learning models

Model name	Accuracy
SVM - Gaussian kernel	73.3%
SVM - Linear kernel	66.4%
SVM - Quadratic kernel	71.4%
KNN - Weighted distance	68.3%
Logistic Regression	68.1%
Linear Discriminant	67.6%

Table 4.1: Classifier Models and Accuracy scores

Table 4.2: Comparison of features and related performance while using SVM to classify into age groups

Group & Method	Features (fts)	Accuracy
SVM-non-linear	Seed based con-	84%
RBF, [162]	nectivity, 200 fts	
SVM-linear ker-	Whole brain FC,	84%
nel, [164]	62 fts	
SVM-Gaussian	Flexibility of	73.3%
kernel	Nodes, 20 fts	

for classification of the participants into young and old (binary classification) based on the flexibility scores as feature vectors for the classifier. Feature reduction with both supervised and unsupervised methods was performed and the resulting reduced feature set was used to train classifiers. Results show that Support Vector Machine (SVM) with Gaussian kernel trained yielded the best classification results. Another redeeming feature of this exercise is that the features (nodes) that are found to be important for classification also align with those identified through the data-driven network measures based analysis.

We expect that validation with two approaches (data-driven and model-based) to address the same question offers an important methodological strategy for future investigations. The findings from the study can help identify the regions that are responsible for the reorganization and maintenance of brain function in healthy ageing [159].

Regions	Network
'Cuneus'	'Visual'
'Cingulum Posterior'	'DMN'
'Cingulum Anterior'	'Control'
'ParaHippocampal'	'Limbic'
'Amygdal'	'Limbic'
'Frontal Superior Orbital'	'Limbic'
'Frontal Inferior Gyrus'	'Control; DMN'
'Cuneus'	'Visual'
'Insula'	'SalVentAttn'
'Hippocampus'	'DMN'
'Cingulum Anterior'	'Control'
'Frontal Inferior Operculum'	'SalVentAttn'

Table 4.3: Common features discovered by ML model and Network Statistics

# Chapter 5

# Characterizing Age-Related Functional Changes and their Association with Cognitive Performance: A Graph Theory Approach<sup>1</sup>

In the previous chapter, we looked at the two ends of the spectrum in healthy ageing. In this chapter, we would like to tackle the transition of ageing that links the changes in the young age group with the old age group.

# 5.1 Introduction

The study of brain networks using network science approaches has gained increasing attention in recent years. Various network measures have been developed to quantify the topological properties of brain networks, including modularity, participation coefficient, within-module degree z-score, and flexibility. These measures have been used to investigate the organization and function of brain networks across different states and conditions, such as during task performance, resting state, and disease [70, 158].

There has also been growing interest in studying the relationship between the brain's static and dynamic network measures. Static network measures are typically computed from the average connectivity matrix across a given period, while dynamic network measures capture the temporal variability in network organization over time. By integrating static and dynamic measures, it is possible to gain a more comprehensive understanding of the brain's functional organization and how it changes over time [85, 160].

The aim of the study is to investigate the reorganization of brain networks as individuals age, particularly during the transition from young to middle-aged to older adults. We plan to achieve this goal by integrating dynamic and static network measures to identify essential brain regions and network properties that undergo changes with age. By utilizing both dynamic and static network measures, the study aims to gain a comprehensive understanding of how brain networks evolve over the ageing process. By doing so, we are able to capture both the stability and flexibility of brain networks and identify specific

<sup>&</sup>lt;sup>1</sup>Under Submission

brain regions that play important roles in cognitive functions. Ultimately, the study seeks to uncover key brain regions and network properties that play a significant role in age-related changes in brain connectivity. By identifying these regions and properties, we hope to shed light on the mechanisms underlying cognitive ageing and potentially discover targets for interventions aimed at supporting healthy brain ageing.

In this study, we used graph theory and network analysis to investigate changes in the brain's functional connectivity in relation to ageing. We analyzed resting-state functional MRI data from 637 healthy adults between the ages of 20 and 89 years and investigated changes in network measures and hub regions.

# 5.2 Methods

## 5.2.1 Network measures

For the purpose of this study, both dynamic and static network measures were considered. **Static network measures**: Nodal measures like participation coefficient and within-module degree z-score as well as global measures like modularity are considered.

**Modularity** refers to the degree of segregation or modular structure within a network. It quantifies how well the nodes of a network can be divided into distinct modules or communities. A higher modularity value indicates a stronger division into separate modules, whereas a lower modularity value suggests a more integrated or less modular network structure.

The **participation coefficient** measures the extent to which a node connects to nodes from other modules or communities within the network. It assesses the degree of integration of a node with nodes outside its own module. A higher participation coefficient indicates that a node has connections that extend beyond its module and is more globally connected, while a lower participation coefficient suggests that a node is predominantly connected within its own module and has fewer connections with nodes from other modules.

Within-module degree z-score is a measure that evaluates the connectivity pattern of a node within its own module relative to the connectivity patterns of nodes in other modules. It compares the degree of a node to the average degree of nodes within the same module and standardizes it by considering the variability of degrees across the entire network. A higher within-module degree z-score indicates that a node has a higher degree of connectivity within its own module compared to other modules.

**Dynamic network measures**: Flexibility is considered to capture the dynamics of community reassignment across different time windows at the nodal level. It quantifies how nodes in a network change their community or module membership over time. A node with a high flexibility value indicates that it frequently changes its community or module membership across different time windows or snapshots of the network. They can act as "bridges" or "hubs" between different communities, allowing for efficient communication and facilitating the integration of information from various sources within the network. On the other hand, low flexibility nodes are often referred to as "specialized" or "local" nodes, as they are more focused on interactions within their own community or module. While nodes with low flexibility may have limited influence on the overall network dynamics, they are important for maintaining the stability and coherence of their specific communities or modules.

Further details regarding the calculation of these scores are presented in Chapter 2.

## 5.2.2 Correlation between network measures

A Pearson's correlation was performed to understand the relationship between the static and dynamic measures. On a nodal level, this correlation is done between the nodes that show a significant difference in the graph/network measures across age groups. When averaged across all nodes, flexibility provides a global estimate of the network's flexibility. This global value is then correlated with modularity. To determine the significance of the correlation between these static and dynamic measures, a p-value threshold of less than 0.05 was used. A p-value below this threshold indicates a statistically significant correlation, suggesting that there is a meaningful relationship between the static and dynamic measures being examined.

# 5.2.3 Calculating the task scores

Detailed analysis of the choice of task scores is presented in Chapter 2. The Benton Test of Facial Recognition is considered for crystallized intelligence [55]. The total score is based on the number of correct responses, with a maximum score of 27.

On the other hand, the Cattell Culture Fair, Scale 2 Form A is used to assess fluid intelligence [56, 57]. The total score is based on the number of correct responses, with a maximum score of 46. For regression purposes, these scores were normalized

# 5.2.4 Choice of regression model

The dependent variables considered are the normalized task scores (Benton and Cattell task scores) and global network measures (flexibility, participation coefficient and within-module degree z-score). Age is considered to be the predictor variable. When fitting the linear model with polynomial terms ranging from 1 to 10, polynomial regression models of increasing degrees are considered. Each additional degree allows for more flexibility in capturing nonlinear relationships between the predictor and the dependent variable. Since higher degrees may capture more intricate patterns in the data but can also lead to overfitting, we use Akaike Information Criterion (AIC), Mean Squared Error (MSE) and R2 metrics along with Occam's razor principle to pick the model that best represents the relation between the independent variable and the predictor.

# 5.2.5 Correlation between task scores and network measures

A straightforward Pearson's correlation is performed to capture the relation between the task scores (Benton and Cattell tasks) and the network measures. Further, to ensure that this correlation was independent of the effect of age,

- 1. A polynomial regression was performed with age as the independent variable and the individual task scores and network measures as the dependent variables.
- 2. The residuals were calculated for both the task scores and network measures. The residuals represent the remaining variation in the variables after removing the effect of age.
- The correlation coefficient between the residuals of each task score and the residuals of each network measure was calculated. This correlation represents the association between the two variables after accounting for age.

# 5.3 Results

The initial findings depict the patterns observed in the network metrics throughout the lifespan, followed by an explanation of the interrelationships between these metrics.

# Age effects on the network measures

## 5.3.1 Modularity changes on age

As age increases, there is a notable rise in global modularity, demonstrating a weak positive Pearson's linear correlation of 0.188 (p<0.05). Nevertheless, the quadratic polynomial fit in Figure 5.1 provides the most accurate representation of the relationship. In both linear and quadratic fits, it becomes evident that as the brain ages, functional modularity, a measure of segregation, increases accordingly.

## 5.3.2 Node-level changes in flexibility

For analysis of the flexibility as a measure of the dynamic behaviour of reorganization, only nodes/ROIs whose flexibility scores exhibited an age effect were considered. Upwards of 50 nodes out of the 116 regions exhibited a significant age effect, indicating that the flexibility scores of these nodes differed across age groups. Specifically, the younger age group had a higher number of nodes with high flexibility scores, while the older age group had a lower number of nodes with high flexibility scores. The group average flexibility scores of the nodes that show significant differences across age groups (p < 0.05 in ANOVA) can be found in A.1. Comparing the subset of 48 nodes showing age effect as well as significant differences across the three age groups, young and middle age groups had a higher range of flexibility scores when compared to the old age group, and the significance was calculated using



(b) A quadratic polynomial fit

Figure 5.1: Modularity vs age where age is the predictor and modularity is the dependent variable. The 95% confidence intervals are plotted for the data points and the predicted values from the linear and quadratic polynomial fit. The quadratic fit explained more variance (adj-rsquare = 0.037) than the linear fit (adj-rsquare = 0.033) with the same RMSE score (0.028).

ANOVA. Nodes belonging to the Default Mode Network and Salience and Ventral Attention Networks demonstrated greater flexibility in the younger age group. In contrast, the older age group showed the least flexibility among the three groups. Nonetheless, within the older age group, the nodes in the Default Mode Network had higher flexibility scores than the other nodes (within the age group). The lower flexibility in the nodes within the Salience and Ventral Attention network in the old age group could be evidence of a more modular network behaviour.

In the older age groups, the nodes that showed significantly higher flexibility compared to the other age groups mainly belonged to SensoriMotor Network. These values and comparisons can be seen in A.1. Further, the flexibilities of nodes that show a significant effect of age can be seen in Fig. A.2. Nodes with flexibility value > 0.4 are labelled in the figure since they represent the higher end of the flexibility scores.

## 5.3.3 Network-level changes in flexibility with age

In the young age group, the visual network has lower flexibility than global flexibility, while the salience and ventral attention, subcortical, and default mode networks have significantly higher flexibility than global flexibility (p < 0.05). These network-level changes are depicted in Fig. 5.2. The young and middle age groups showed a similar trend across network flexibility (p < 0.05 in a one-way ANOVA). However, the flexibility scores of the networks in the middle age group are lower than that observed in the young age group (p < 0.05). However, there is a deviation from this trend in the old age group. Specifically, the flexibility of the Visual network is observed to increase in the old age group, while that of the Subcortical and Salience and ventral attention networks show a significant decrease (p < 0.5 in a one-way ANOVA individually on the respective network's flexibility, it is still far lower than that of the other networks as well as the mean global flexibility.

## 5.3.4 Participation coefficient changes with age

The participation coefficient is used to assess the degree of integration at the nodal level. Similar to flexibility, it detects the extent of connection a node has to other networks' nodes. A majority of the regions that showed a significant difference, in a one-way ANOVA, across age groups belong to the Sensorimotor and Visual networks. A detailed list of the regions can be found in A.5.

In fact, all the regions observed in Sensorimotor and Visual networks that showed differences showed the highest participation coefficient in the old age group. Regions of the Default Mode Network like the Orbitofrontal region and Temporal regions see a much lower participation coefficient in the old age group compared to the other age groups. The network-level participation coefficient changes, which is the average of the participation coefficient of nodes showing age related effect, across age groups can be observed in 5.3.



Figure 5.2: Network changes in flexibility scores across age group. The changes across age groups within each network is significant (p < 0.05). The differences across networks within the same age group is significant (p < 0.05). While young and middle age groups show a similar decreasing trend across networks, there is a deviation from this trend observed in old age groups. There is a consistent increase/decrease toward the global flexibility scores in the flexibility scores of the networks in the older age groups.



Figure 5.3: Network average participation coefficient of the young, middle and old age groups. Visual, SensoriMotor and Default Mode network showed significant difference across age groups (p < 0.05)

#### Capturing similarity of participation scores across age groups

In order to capture the similarity of the participation coefficient pattern across age groups, mutual information was calculated for young-middle, young-old and middle-old as seen in table 5.3. Further, it was normalized across each age group in focus to compare. In the young age group, the participation coefficient showed the most resemblance to the middle age group as compared to the old age group. This was also seen in the middle age group, where the mutual information captured with the young age group's participation coefficient was higher than that with the older age group. In the older age group, however, the mutual information captured by the young and middle age groups' participation coefficient was much lower, with the younger age group having higher mutual information.

## 5.3.5 Within-module degree z-score (WMD) across age groups

This network measure is calculated as a z-score. Hence, nodes that have a negative score indicate that they're unlikely to be in the assigned functional module [70]. To intuitively understand this conclusion, the within-module degree of a node is the number of links/edges passing through the node in question. The edges/links considered in the calculation are from the nodes that belong to the same community/module as the node in question. Finally, this degree is z-score normalized to obtain the WMD score. Hence, a node with very low score would have comparatively few links/edges from other nodes that pass through the node in question.

The results from a one-way ANOVA to identify the nodes that show a significant difference (p < 0.05)

in the within-module degree z-scores across age groups A.6. Visual and Subcortical networks show an significant difference across age groups 5.4, where both the absolute values decrease.



Figure 5.4: Network average within-module degree (z-score) of the young, middle and old age groups. This figure showcases the average within-module degree (z-score) of various networks within the young, middle, and old age groups. The plot highlights significant differences observed across age groups, specifically in the visual and subcortical networks (p<0.05).

## Capturing similarities of within module degree z-scores across age groups

Mutual information was computed for the within-module degree z-scores across age groups. Then for each of the age group, this MI value was normalized. This can be seen in table 5.4. The normalized MI values are very low for all pairs of age groups. Since these similarities after L2-normalization are very low, using within-module degree as a feature for classification would be desirable.

# 5.3.6 Correlation between dynamic and static network measures

## Modularity vs Global Flexibility

A negative correlation between modularity and global flexibility is observed in all age groups. This is shown in Fig. 4.2. This correlation is statistically significant (p < 0.05). [18, 150]. The modularity increases as one goes from young to old while flexibility decreases Fig. 5.5.



(c) Old age group

Figure 5.5: Modularity vs global flexibility. The young, middle and old age groups show a negative correlation between flexibility and modularity, as expected. Rho, the correlation between modularity and global flexibility, is the highest in the case of old age group. The x-axis represents the flexibility scores and the y-axis represents the modularity values.

#### Network flexibility vs Modularity

In the young age groups, Salience and Ventral Attention network as well as the SensoriMotor network shows a negative correlation with modularity 5.12. In the middle age groups, the Default Mode network as well as the Salience and Ventral Attention network show a negative correlation between flexibility and modularity 5.13. However, in the older age groups, there is a participation in the contribution to the negative correlation observed between global flexibility and modularity. All the networks except the visual network seem to show a significant negative correlation between the flexibility scores and modularity (p < 0.05). This can be seen inFig. 5.14.

## Network flexibility and participation coefficient

Calculating Pearson's correlation across all ages involves considering the relationship between network participation coefficient (PC) and flexibility by aggregating these scores from individuals across the entire age spectrum. This analysis examines the general trend observed when age is treated as a continuous variable. In this case, the average values of PC and flexibility across nodes within each resting-state network are used. The findings indicate that the Visual, Sensorimotor (SMN), Subcortical, and Default Mode Network (DMN) show a weak positive correlation with flexibility. The statistical significance of this correlation is determined using a significance level of p <0.05 5.6.

On the other hand, calculating Pearson's correlation within specific age groups (such as young, middle, and old) involves examining the relationship between PC and flexibility within each age category separately. In this analysis, the focus is on investigating how the correlation varies within distinct age groups. The results reveal that the DMN and Visual network exhibit a significantly weak positive correlation between PC and flexibility within the young age group 5.15. The SMN and Visual network show a weak positive correlation in the middle age group 5.16. In contrast, the DMN, Salience, Ventral Attention, and SMN networks display a weak positive correlation with flexibility in the old age group 5.17.

These findings emphasize a weak positive relationship between network PC and flexibility, which holds when considering all ages collectively as well as within individual age groups (highest correlation < 0.3).

#### Network flexibility and within-module degree z-score

Calculating Pearson's correlation across all ages involves examining the relationship between network within-module degree z-score (WMD) and flexibility by considering data from individuals across the entire age range. Similar to the previous section, this analysis examines the general trend observed when age is treated as a continuous variable. The average values of WMD and flexibility across nodes within each resting-state network are used. The results indicate a weak negative correlation between WMD and flexibility for the Visual, Salience and Ventral Attention Network, Subcortical, and Default



Figure 5.6: Correlation Between Network-Averaged Participation Coefficient and Flexibility Across All Ages. The plot shows Pearson's correlation scores between the network-averaged participation coefficient (PC) and flexibility. Only correlations with p-value<0.05 are presented to account for statistical significance.



Mode Network (DMN) 5.7. The statistical significance of this correlation is determined using a significance level of p < 0.05.

Figure 5.7: Correlation Between Network-Averaged Within-Module Degree z-score and Flexibility Across All Ages. The plot illustrates the correlation between the network-averaged within-module degree z-score and flexibility. The within-module degree z-scores were scaled using a linear transformation to fit between -1 and 1. Only correlations with p-value <0.05 are presented.

Conversely, Pearson's correlation is calculated within specific age groups (young, middle, and old). This analysis focuses on understanding how the correlation varies within distinct age groups. The findings reveal that within the young age group, the Salience and Ventral Attention Network, Subcortical and Visual network show a significantly weak negative correlation between WMD and flexibility 5.18. In the middle age group, the DMN, Salience and Ventral Attention Network, Subcortical and Visual network exhibit a weak negative correlation 5.19. In the old age group, the DMN, Subcortical, Visual, and Sensorimotor (SMN) networks display a weak negative correlation with flexibility 5.20.

Overall, these findings suggest a weak negative relationship between network WMD and flexibility when considering all ages as a continuous variable and within different age groups.

# 5.3.7 Changes in provincial hubs across age

The table A.9 provides information on the nodes that are considered provincial hubs. These nodes have high within-module degrees and low participation coefficients, which means they are important for local connections within their respective modules. The table indicates that the provincial hubs tend to be located in the SMN, Visual, and Subcortical networks in the young and middle age groups. This suggests that these networks may constitute the rigid core, as these nodes are more tightly connected within their respective network and less connected to other brain regions.

The table also provides information on the age-related changes in network connectivity for different brain regions. For example, in the SMN network, some nodes considered provincial hubs in younger individuals or middle-aged cease to be so in older individuals. This suggests that the local connectivity within the SMN network decline in old age. Occipital regions remain provincial hubs across all age groups. Figure 5.8 shows the age category-wise distribution of the nodes. For example, a greater percentage of the Young age group in the figure signifies that the provincial hubs show more activity during the younger ages and have relatively lower activity during older ages. This implies that the Visual network's internal connectivity may decrease as individuals age, specifically for the regions crucial for connecting within the module.

Overall, the hubs reported in table A.9 have a greater impact on integrating information flow within networks in cognitive tasks and brain functions most prominent within their respective age groups.

# 5.3.8 Changes in connector hubs across age

According to the table A.8, the regions associated with attention, memory, and visual processing show changes with age.

In contrast to that observed in provincial hubs in the previous section, most nodes presented in the table turn into connector hubs in the older age groups as seen in Figure 5.9. Regions like Frontal-Inferior-Triangularis (Frontal-Inf-Tri), Middle Temporal gyrus (Temporal-Mid) and Hippocampus remain connector hubs across all age groups. These regions are primarily involved in higher-order processes, language-related tasks, visual and auditory processing for spatial navigation and memory processing. From table A.8 and Figure 5.9, the old age group has a higher percentage of connector hubs than the middle or young age groups, which may suggest that these brain regions are more actively engaged in integrating information flow across different brain networks in older individuals.



Figure 5.8: Analysis of Provincial Hubs' Age Categories. The pie chart depicts the distribution of provincial hubs based on age categories, revealing the percentage of hubs exhibiting distinct age-related activity patterns. It showcases hubs that are exclusively active in a single age group, hubs active across multiple age groups, and hubs active across all three age groups. Generated from A.9



Figure 5.9: Analysis of Connector Hubs' Age Categories. The pie chart depicts the distribution of connector hubs based on age categories, revealing the percentage of hubs exhibiting distinct age-related activity patterns. It showcases hubs that are exclusively active in a single age group, hubs active across multiple age groups, and hubs active across all three age groups. Generated from A.8
#### 5.3.9 Hemispherical asymmetry in regions with ageing

There are hemispherical differences observed in the study. For example, in the table for connector hubs, table A.8, the frontal regions show asymmetry in all age groups. However, more hemispherical symmetry is observed in connector hubs present only in the older age groups. Regions in the frontal cortex, hippocampus and temporal gyrus however show asymmetry in old age. For example, the changes in connectivity in the right 'Temporal-Mid-R' region, which becomes a connector hub in old age as opposed to 'Temporal-Mid-L', may reflect compensatory mechanisms in the right hemisphere for maintaining attentional performance. Similarly, in the table for participation coefficient, table A.9, the regions that are provincial hubs in the older age groups display this symmetry in all the corresponding age groups. These hemispherical differences suggest that age-related changes in brain connectivity may not be uniform across the brain but rather differ between the left and right hemispheres for the young and middle age groups. These differences may reflect the specialization of different brain regions for specific cognitive functions.

#### 5.3.10 Age-related changes in task-scores

Task scores show a significant (p-value < 0.005) correlation with age. As shown in figure 5.10, Cattell and Benton's task performance declines with age and displays a rather strong negative correlation. The Cattell task and age have a Pearson's correlation value of -0.650, while the Benton task decreases with age with a strength of -0.452. While a linear fit does capture strong correlations of the task scores with age, the best-fit model is a quadratic model, as seen in Table 5.2.

#### 5.3.11 Relation between network measures and cognitive performance

The tables A.10, A.12 and A.11 contain the correlations between various network measures (flexibility, within module degree z-score and participation coefficient) and the task scores (Benton and Cattell). This analysis was done at a node level. There are no strong correlations for both tasks with any of the task measures. To be precise, the range of correlation for each of the network measures across both tasks is as follows:

- Participation Coefficient: From -0.218 to 0.270.
- Within-module degree z-score: From -0.164 to 0.197.
- Flexibility: From -0.159 to 0.271.

As shown in the table 5.1, for both tasks, none of the network measures considered on a global level (flexibility, participation coefficient, within-module degree) showed significant correlations with task performance, except for a weak positive correlation between flexibility and the Cattell task (r = 0.093, p < 0.05). As described in Chapter2, the residuals from the regression analysis were plotted to observe any correlations between the task scores and different network measures after removing the effect of



Figure 5.10: Scatter plot showing the relationship between Cattell and Benton task scores (y-axis) and age (x-axis). There is a strong negative correlation between both the task scores and age. The p-value is highly significant (p < 0.05), suggesting a significant association in both cases.



Figure 5.11: This plot illustrates the residuals in relation to task performance (Benton and Cattell tasks) and network measures (Flexibility, Participation Coefficient, and Within-Module degree z-score). The plot also has the average global value of the network measures.

age. The best-performing regression models are presented in table 5.2. Figure 5.11 are the residual plots of the tasks vs network measures. From the plot, only Cattell task scores correlate significantly, albeit weak, with global flexibility.

## 5.4 Discussion

#### 5.4.1 Modularity vs Global Flexibility

The brain dynamics can be represented according to the theory of attractor states. Attractor states are the stable states which can be represented as Functional Connectivity configurations. Flexibility measures the transitions between the attractor states while modularity defines the depth of the attractor states [167, 168, 161]. Following this intuition, flexibility is expected to show a negative correlation with modularity. As expected, all the age groups show a negative correlation between modularity and flexibility, as shown in Fig. 4.2. This correlation is statistically significant (p < 0.05). [18, 150]. It is theorized that in the older age groups, the modularity remains high because of the high connection weights instead of the sheer number of connections. At the same time, due to dedifferentiation, other nodes are expected to participate in more number of functional modules [148, 20, 140].



bility

(c) Modularity vs SensoriMotorNetwork flexibility

Figure 5.12: Correlation between Modularity and Flexibility in Networks Among Young Age Groups. Networks whose flexibilities show a negative correlation with modularity in Young age groups. The x-axis represents the flexibility scores and the y-axis represents the modularity values.

#### 5.4.2 Node-level changes in flexibility

ity

Greater than 50 nodes showed a significant age effect when flexibilities were compared across all ages. The younger age group witnessed a greater number of nodes with high flexibility than the other age groups. This could be due to the larger integration observed as one is still 'learning' meaningful connections and optimizing the segregation-integration balance [170]. On the other hand, the old age group witnessed a lower number of nodes that exhibit high flexibility scores. This could be evidence of a small number of nodes being responsible for the integration while maintaining the efficiency of the segregated modules.

However, when the flexibility scores were compared, younger and middle age groups showed a wider range of flexibility scores when compared to the old age group A.1. This was observed in nodes that belong to Default Mode Network and Salience and Ventral Attention Networks. However, in spite of the age-related decline of Default Mode Network that has been shown in previous literature, the intranetwork connections are expected to be higher in the older age groups. That being said, the flexibility scores of the nodes comprising the Default Mode Networks were on the higher end relative to the scores of the other nodes in the old age group[126]. In the salience subsystems, it has been shown that the ventral salience subsystem shows an increase in connectivity in older age groups [171]. The lower flexibility in the nodes that belong to the Salience and Ventral Attention network in the old age group could be evidence for a more modular behaviour of this network.

In the older age groups, the nodes that showed a significantly higher flexibility compared to the other age groups mainly belonged to SensoriMotor Network. Previous literature has reported an increase in the intra-network connections observed in the nodes comprising the SensoriMotor Network. In addition, the integration of sensory information is optimized with age. [172, 22].



Figure 5.13: Global and Network wise flexibility correlation with modularity in the middle age group. The x-axis represents the flexibility scores and the y-axis represents the modularity values.



Figure 5.14: Global and Network wise flexibility correlation with modularity in the old age group. The x-axis represents the flexibility scores and the y-axis represents the modularity values.

#### 5.4.3 Network-level changes in flexibility across age

The flexibility of different brain networks changes with age, and this change is not uniform across all networks 5.2. Specifically, in the young age group, the visual network has lower flexibility compared to other networks such as the salience and ventral attention, subcortical, and default mode networks which have significantly higher flexibility than the mean global flexibility. This trend is also observed in the middle age group, although the overall global flexibility was lower than in the young age group. However, in the old age group, there was a deviation from this trend and the individual networks tended to converge towards global flexibility 5.2.

Furthermore, the study found that the flexibility of the visual system increased in the old age group compared to the other age groups, while the subcortical and salience and ventral attention networks showed a significant decrease. The decrease in flexibility of the subcortical and salience and ventral attention networks may suggest a decline in their ability to respond to changes in the environment, which may contribute to age-related cognitive decline. While the visual network still seems to make up the rigid core in the older age group, it also appears to be more flexible than the other age groups, implying a possible overactivation as a part of the compensatory mechanisms [30]. This suggests that the nodes of the visual network are more likely to co-activate with nodes from other networks, which still have higher flexibility than the mean global flexibility in the respective group but show a significant decrease in the old age group.

This is a deviation from the PASA theory that suggests the overactivation of the prefrontal cortex to compensate for the decrease in occipital activations in old age groups compared to young age groups [15, 173]. However, it is worth noting that the PASA theory focuses on age-related changes in specific regions rather than in resting-state networks. Hence, the observed increase in flexibility of the visual system in older adults may indicate a compensatory mechanism that is not captured by the PASA theory. The finding that the visual network becomes more strongly connected with age is in line with several previous studies that have reported age-related increases in functional connectivity within visual regions [174, 175].

#### 5.4.4 Network flexibility vs Modularity

The negative correlation between flexibility and modularity suggests that as brain networks become more flexible, they become less modular, meaning that they are less distinct and more interconnected [168, 167]. This may indicate that the brain networks are becoming more integrated and may be involved in more complex and integrated cognitive processing. Another way to look at it is a negative correlation with flexibility suggests that as subnetworks/modules become more specialized, they become less able to adapt to changes in other parts of the brain.

In young and middle-aged adults, networks such as the Salience and Ventral Attention network, Default Mode network and the SensoriMotor network show a negative correlation between flexibility and modularity (statistically significant correlation), suggesting that these networks may be more specialized and less adaptable (Figures 5.12,5.13. However, in older adults (figure 5.14, there is a more general trend towards a negative correlation between flexibility and modularity across all networks, suggesting that ageing may be associated with a decline in the ability of networks to adapt to changes in other parts of the brain.



Figure 5.15: Correlation between flexibility and participation coefficient at the network level in the young age group. All correlations shown are statistically significant (p-value < 0.05). The correlation analysis reveals a weak positive relationship between network-wise flexibility and participation coefficient across all networks. This suggests that as the participation coefficient increases, indicating a higher level of integration with other nodes in different networks, the flexibility of the node in community assignment also tends to increase. However, the observed correlation is not very strong or consistent, indicating that other factors may also influence this relationship.

#### 5.4.5 Participation coefficient

The participation coefficient measures how well a node in a network is connected to different modules or communities within the network. A high participation coefficient indicates that a node is wellconnected to different modules, while a low participation coefficient indicates that a node is primarily connected to a single module [70].

In this context, the positive correlation between the participation coefficient and flexibility suggests that regions with a higher participation coefficient have a more flexible connection pattern and can easily switch between different functional networks 5.6.



Figure 5.16: Correlation between flexibility and participation coefficient at the network level in the middle age group. All correlations shown are statistically significant (p-value < 0.05). The correlation analysis reveals a weak positive relationship between network-wise flexibility and participation coefficient across all networks. This suggests that as the participation coefficient increases, indicating a higher level of integration with other nodes in different networks, the flexibility of the node in community assignment also tends to increase. However, the observed correlation is not very strong or consistent, indicating that other factors may also influence this relationship.



Figure 5.17: Correlation between flexibility and participation coefficient at the network level in the old age group. All correlations shown are statistically significant (p-value < 0.05). The correlation analysis reveals a weak positive relationship between network-wise flexibility and participation coefficient across all networks. This suggests that as the participation coefficient increases, indicating a higher level of integration with other nodes in different networks, the flexibility of the node in community assignment also tends to increase. However, the observed correlation is not very strong or consistent, indicating that other factors may also influence this relationship.



Figure 5.18: Network-wise flexibility correlation with within-module degree z-score in the young age group

The results suggest that the regions within the sensorimotor and visual networks tend to be more flexible and participate more in communication between different brain regions as individuals age, which may reflect compensatory mechanisms to maintain cognitive function 5.16,5.17.

In contrast, regions within the default mode network, such as the orbitofrontal and temporal regions, show a lower participation coefficient in older age groups, indicating a decreased ability to integrate information from other brain regions A.5.

The mutual information analysis provides a measure of how similar the participation coefficient patterns are across age groups. The observation that younger and middle age groups show higher mutual information with each other compared to the older age group suggests that the participation coefficient patterns in older adults are more distinct from those in younger and middle-aged adults[175], table 5.3.

#### 5.4.6 Within-Module z-degree

The within-module degree (WMD) measure captures the degree of interconnectedness of nodes within their assigned functional module. The WMD score is z-score normalized, and nodes with negative scores indicate that they are unlikely to belong to the assigned functional module. In the present study, a high WMD score indicates that a node has many links/edges passing through it from other nodes within the same functional module.

The WMD measure is negatively correlated with flexibility, which suggests that nodes with high within-module degree are less flexible in their functional connectivity 5.18,5.7.

The mutual information computed for WMD scores across age groups indicates that the WMD pattern of the young age group is more similar to that of the old age group than the middle age group. Similarly, the middle age group shows a WMD pattern more similar to the old age group. However, the similarities observed after normalization are low 5.4.



Figure 5.19: Network-wise flexibility correlation with within-module degree z-score in the middle age group



Figure 5.20: Network-wise flexibility correlation with within-module degree z-score in the old age group

#### 5.4.7 Provincial hubs

The number of provincial hubs that decline with age are not uniform across the resting state networks as seen in table A.9. This suggests that the specialization of brain regions for specific cognitive processes may change with age, with some regions becoming more specialized (provincial) and others becoming less specialized.

Across all age groups, the occipital regions remained localized centres, suggesting that these areas might play a significant role in maintaining visual processing [173]. This observation aligns with previous studies indicating that older individuals tend to develop compensatory mechanisms in these occipital regions, depending more on cognitive control to sustain their cognitive performance. Specifically, the older age group may utilize top-down cognitive control to make up for declines in bottom-up visual processing [15]. The finding that the SMN network becomes less strongly connected with age is also consistent with previous research, which has shown age-related declines in motor function and changes in the functional connectivity of motor-related regions [176, 177].

Moreover, in the provincial hubs of the Visual and SensoriMotor networks, the within-module degree z-scores were positively associated, albeit weak, with cognitive performance, suggesting that the preservation of these hubs may be important for maintaining cognitive function with age A.14.

#### 5.4.8 Connector Hubs

The study found that the most of the connector hubs were identified in the older age group (Figure 5.9). Majority of these nodes belonged to the Visual and Subcortical networks. This suggests that older adults may rely more on visual and attention networks for compensatory mechanisms in cognitive processing. The persistence of connector hubs in the hippocampus, frontal regions, and temporal regions across all age groups suggests the importance of these areas in maintaining cognitive abilities throughout the ageing process. The frontal-inferior-triangular region is associated with language-related tasks and higher-order cognitive processes [178, 179, 180, 181]. The temporal-mid region is involved in auditory processing and memory functions [182, 183]. The hippocampus plays a crucial role in spatial navigation and memory processing [184, 185, 186].

The connector hubs however showed a decline in cognitive task performance with increasing participation coefficient or within-module degree z-scores for various brain regions within the Salience and Ventral Attenion as well as the Subcortical networks A.13

Overall, the identification of connector hubs in certain brain regions across all age groups highlights the critical role of these regions in integrating information across different brain regions and in supporting cognitive processes.

#### 5.4.9 Hemispherical asymmetry in activations

Hemispherical asymmetry in the brain has been a topic of interest in neuroscience for several decades. The left and right hemispheres of the brain are structurally and functionally different, and this lateralization plays a crucial role in various cognitive processes such as language, spatial awareness, and emotional processing [187].

Studies have found that language processing is predominantly lateralized to the left hemisphere, with the left inferior frontal gyrus and left superior temporal gyrus being particularly important. In contrast, spatial awareness and emotional processing are often lateralized to the right hemisphere [188].

Moreover, hemispherical asymmetry may change with age. For example, some studies have reported that hemispherical asymmetry in language processing may decrease with age, as older adults tend to rely more on the right hemisphere to compensate for declines in left hemisphere function. Similarly, hemispherical asymmetry in emotional processing may also change with age, with some studies suggesting that older adults may show reduced lateralization in emotional processing compared to younger adults [144]. The study found that the younger and middle-aged groups exhibited asymmetry in the connector hubs, indicating specialized functions. However, symmetry was observed in the hubs specific to older age groups, suggesting the involvement of compensatory mechanisms. The reason for selecting connector hubs for comparison is that they signify the integration of information across various networks. A.8,A.9.

#### 5.4.10 Task scores with age

Previous studies have indicated a decline in face recognition with age. Fluid intelligence is believed to reflect the functioning of the frontoparietal multiple-demand system in constructing mental control programs for complex activities [189]. The strong negative correlation between task scores and age aligns with previous literature.

#### 5.4.11 Relation between task scores and network measures of rs-fMRI

- 1. The lack of strong correlations between task scores and resting-state functional connectivity (FC) at the node level suggests that the cognitive or behavioural processes assessed by the tasks may not be directly reflected in the functional connectivity patterns of the resting-state brain. This finding is consistent with recent research indicating that functional connectivity measures may not always align closely with specific cognitive functions or task performance [190]. It suggests that the relationship between task performance and resting-state FC may be more complex and involve higher-order network properties or distributed brain networks rather than individual nodes.
- 2. Despite a significant correlation between Cattell scores and global flexibility computed on restingstate FC, the observed correlation was very weak. Global flexibility measures the ability of a network to reconfigure its functional connections dynamically. The weak correlation indicates that Cattell scores explain only a small portion of the variance in global flexibility. This finding aligns with previous studies highlighting the multifaceted nature of the relationship between cognitive abilities and brain network dynamics [157, 191, 192].

3. The continuation of the trend, with weak correlations between task scores and resting-state FC, even after regressing out age as a factor, suggests that age-related changes in brain function do not fully account for the observed lack of strong associations. This finding is consistent with recent literature demonstrating that age-related differences in functional connectivity may not solely explain the relationship between cognitive performance and resting-state FC [175, 193, 194, 126]. It implies that other factors, such as task specificity, individual differences, or additional unmeasured variables, may contribute to the weak correlations between task scores and resting-state FC beyond the influence of age.

In summary, the findings suggest that the relationship between cognitive abilities, task performance, and brain network dynamics is complex and influenced by multiple factors beyond age and nodal-level connectivity.

Furthermore, it is important to note that resting state FC explains approximately 70% of the variance in task-based FC [49]. This finding underscores the substantial influence of intrinsic brain connectivity on task-related brain activity. The high proportion of variance explained by resting state FC suggests that the brain's intrinsic functional architecture serves as a foundational framework upon which taskspecific networks are built. However, it is crucial to recognize that the remaining 30% of the variance in task-based FC is likely attributed to task demands, cognitive processes, and other factors that are not captured solely by resting state FC.

### 5.5 Conclusion

In conclusion, our study aimed to understand the reorganization of brain networks during the ageing process, specifically examining the transition from young to middle-aged to older adults. Through the integration of dynamic and static network measures, we identified significant changes in brain connectivity associated with ageing.

Firstly, we observed that certain brain regions undergo changes in connectivity as individuals age. Notably, we found an increase in modularity with age, indicating a greater degree of functional specialization in the ageing brain. In contrast, there was a decrease in flexibility with age, suggesting reduced adaptability to changing cognitive demands.

Additionally, we investigated the relationship between flexibility and modularity, revealing a negative correlation in all age groups, with the strongest correlation observed in the young and old age groups. This finding suggests that as the brain becomes less modular, it becomes more flexible in its organization. Furthermore, the participation coefficient and within-module degree z-scores, complementary centrality measures characterizing node diversity and localized degree, indicated that nodes with higher flexibility scores are more likely to be integrative connector hubs rather than provincial hubs.

Our analysis of regional network measures highlighted significant differences, including decreased participation coefficient in several frontal and parietal regions, and increased participation coefficient

Task	Measure	Correlation
Cattell	Flexibility	r = 0.093, p<0.05
Cattell	Participation coefficient	$r \approx 0$ , p>0.05
Cattell	Within-Module Degree (z-score)	r = 0.017, p>0.05
Benton	Flexibility	r = 0.025, p>0.05
Benton	Participation coefficient	r = 0.028, p>0.05
Benton	Within-Module Degree (z-score)	r = 0.013, p>0.05

Table 5.1: Partial Correlations between Global Network Measures and Task Performance Scores, Controlling for Age. This table presents the partial correlations between global network measures and task performance scores for two tasks: Cattell and Benton. The analysis takes age into account as a controlled factor to isolate the relationship between network measures and task performance beyond the influence of age.

in several frontal and temporal regions. These findings suggest alterations in information integration across different brain regions with ageing.

Further exploration of hub regions revealed that provincial hubs primarily belonged to the younger age group, while connector hubs predominantly belonged to the older age group. We also discovered hemispheric differences in network measures, with the right hemisphere exhibiting greater local efficiency (provincial hubs). This suggests that age-related changes in brain connectivity may not be uniform across the brain and may differ between the left and right hemispheres.

Regarding cognitive abilities and brain network dynamics, we found the absence of strong correlations between task scores and network measures at the node level, weak correlations between Cattell scores and global flexibility, and persistence of these findings even after accounting for age. These results underscore the complexity of the relationship between cognitive abilities, task performance, and brain network dynamics, indicating that factors beyond age and nodal-level connectivity play significant roles in shaping their associations.

Overall, our study contributes to a deeper understanding of the reorganization of brain networks during ageing. The identified changes in network measures and hub regions may be crucial in explaining age-related declines in cognitive performance. These findings have potential implications for the development of interventions aimed at supporting healthy cognitive ageing by targeting specific brain regions and network properties. However, further research is needed to elucidate the underlying mechanisms behind these age-related changes and their impact on cognitive function.

Regression model	MSE	R2	AIC
flex $\sim age^2$	0.005	0.080	-1371
PC ~age	0.012	0.006	-868
WMD ~age	0.010	0.032	-967
CatNorm $\sim age^2$	0.557	0.446	1220
BenNorm $\sim age^2$	0.778	0.227	1439

Table 5.2: Best fit of Regression Models Based on MSE, R2, and AIC. The table showcases the evaluation of multiple regression models using Mean Squared Error (MSE), R-squared (R2), and Akaike Information Criterion (AIC). The dependent variables examined include flexibility (flex), participation coefficient (PC), within-module degree z-score (WMD), normalized Cattell task scores (CatNorm), and normalized Benton task scores (BenNorm). The network measures considered are calculated at the global scale. The predictor considered is age. The models displayed in the table are selected based on their lower MSE and AIC values, indicating superior predictive accuracy and goodness of fit.

Group 1	Group 2	MI	Normalized-MI
Young'	Young'	1.651	0.932
Young'	Middle'	0.591	0.334
Young'	Old'	0.248	0.140
Middle'	Young'	0.591	0.362
Middle'	Middle'	1.502	0.921
Middle'	Old'	0.236	0.145
Old'	Young'	0.248	0.173
Old'	Middle'	0.236	0.164
Old'	Old'	1.396	0.971

Table 5.3: Mutual Information (MI) and Normalized Mutual Information of Participation Coefficients Between Age Groups. This table showcases the mutual information (MI) and normalized mutual information values of participation coefficients calculated between different age groups. The mutual information quantifies the association between Group 1 and Group 2, while the normalized value is computed relative to the focused group, Group 1. The table offers insights into how participation coefficients vary and are related across age groups

Group 1	Group 2	MI	Normalized-MI
Young'	Young'	0.135	1.000
Young'	Middle'	0.001	0.008
Young'	Old'	0.002	0.016
Middle'	Young'	0.001	0.005
Middle'	Middle'	0.232	0.987
Middle'	Old'	0.038	0.161
Old'	Young'	0.002	0.006
Old'	Middle'	0.038	0.097
Old'	Old'	0.386	0.995

Table 5.4: Table illustrating the mutual information (MI) and normalized mutual information values of within-module degree z-score calculated between different age groups. The mutual information represents the association between Group 1 and Group 2, while the normalized value is calculated across the focused group, Group 1.

## Chapter 6

## **Conclusion and Future Work**

## 6.1 Conclusion

In conclusion, this thesis sought to investigate the brain dynamics and changes in connectivity associated with ageing. Chapter 4 focused on the comparison between young and old age groups, while Chapter 5 expanded the analysis to include young, middle, and old age groups, treating age as a continuous variable. By examining both discrete age groups and the continuous nature of ageing, this thesis provided a comprehensive understanding of how the brain's functional stability is maintained amidst structural decline.

In Chapter 4, a data-driven analysis using statistical and graph-theoretic measures was employed to study modular segregation and integration in the brain. The findings revealed characteristic nodes that constituted a stable core and flexible periphery in the young and old age groups. Notably, regions within the Default Mode network (DMN) exhibited a negative correlation with modularity in the old age group, while regions from the Limbic, SensoriMotor (SMN), and Salience networks showed a positive correlation. Machine learning models based on flexibility scores further confirmed the relevance of these regions, aligning with the data-driven network analysis. This integration of data-driven and model-based approaches provides a promising methodological strategy for future investigations.

Chapter 5 age-related changes in brain connectivity and network properties. It found an increase in modularity with age, indicating greater functional specialization in the ageing brain, along with a decrease in flexibility, suggesting reduced adaptability to changing cognitive demands. The negative correlation between flexibility and modularity across all age groups implies that as the brain becomes less modular, it becomes more flexible in its organization. Certain brain regions showed significant alterations in connectivity, with increased participation coefficient in some frontal and temporal regions and decreased participation coefficient in several frontal and parietal regions. Hemispheric differences were also observed, with the right hemisphere displaying greater local efficiency (provincial hubs), suggesting that age-related connectivity changes may vary between hemispheres.

The complexity of the relationship between cognitive abilities, task performance, and brain network dynamics was highlighted in Chapter 5. The absence of strong correlations between task scores and

network measures at the nodal level, as well as the weak correlation between Cattell scores and global flexibility, underscored the multifaceted nature of these associations. Age alone could not account for the observed dynamics, suggesting the involvement of other factors in shaping the relationship between cognition and brain network measures.

These findings significantly contribute to our understanding of the reorganization and maintenance of brain function in healthy ageing. The identified brain regions and their connectivity changes shed light on the transition from modularity to flexibility in the ageing brain. Moreover, this research highlights the need for further investigation into the intricate associations between cognitive abilities, task performance, and brain network measures. Future studies could explore additional cognitive or behavioral measures, examine dynamic changes in network connectivity during task performance, or investigate other potential factors influencing the relationship between cognition and brain network dynamics. By advancing our understanding of these complex relationships, we can gain insights into the mechanisms underlying cognitive abilities and the role of brain network dynamics in supporting cognitive function. Such knowledge may have implications for developing interventions and strategies to enhance cognitive performance and promote healthy brain ageing.

In conclusion, this thesis has provided valuable insights into the brain dynamics and changes in connectivity associated with ageing. Through a comprehensive analysis of discrete and continuous age groups, the findings contribute to our understanding of the reorganization and maintenance of brain function in healthy ageing. The identified brain regions and their connectivity changes underscore the transition as the brain ages. Further research is warranted to unravel the underlying mechanisms and their impact on cognitive function. Ultimately, this knowledge has the potential to inform interventions and strategies for enhancing cognitive performance and promoting healthy brain ageing.

# Appendix A

# Appendix A

Table A.1: Brain Regions with Significant Age-Related Differences in Flexibility Values. The nodes in this table exhibit notable variations in flexibility scores across different age groups. The columns 'Group - max' and 'Group - min' indicate the age groups with the highest and lowest flexibility values for each respective brain region. These regions have previously been shown to be significantly influenced by age.

Region Name	Young group	Middle	Old	group	Group - max	Group - min	Network
	mean	group mean	mean				
SFGdor.L	0.360	0.310		0.320	young	middle	DMN
ORBsup.L	0.430	0.410		0.380	young	old	DMN
ORBsup.R	0.430	0.420		0.390	young	old	DMN
IFGoperc.L	0.410	0.380		0.350	young	old	SalVentAttn
IFGoperc.R	0.380	0.340		0.340	young	old	SalVentAttn
IFGtriang.L	0.410	0.380		0.350	young	old	SalVentAttn
IFGtriang.R	0.380	0.340		0.340	young	old	SalVentAttn
ORBinf.L	0.460	0.410		0.380	young	old	SalVentAttn
ORBinf.R	0.430	0.400		0.380	young	old	SalVentAttn
OLF.R	0.500	0.490		0.420	young	old	SMN
ORBsupmed.L	0.500	0.490		0.440	young	old	DMN
ORBsupmed.R	0.460	0.430		0.390	young	old	DMN
REC.L	0.490	0.450		0.430	young	old	DMN
REC.R	0.470	0.460		0.410	young	old	DMN
DCG.L	0.370	0.350		0.310	young	old	Subcortical
DCG.R	0.350	0.320		0.300	young	old	Subcortical
PCG.L	0.460	0.450		0.400	young	old	DMN
PHG.L	0.430	0.400		0.350	young	old	Subcortical

Region Name	Young group	Middle	Old	group	Group - max	Group - min	Network
	mean	group mean	mean				
PHG.R	0.420	0.380		0.360	young	old	Subcortical
AMYG.L	0.480	0.460		0.420	young	old	Subcortical
MOG.R	0.260	0.230		0.220	young	old	Visual
SPG.L	0.320	0.290		0.260	young	old	SMN
SPG.R	0.310	0.280		0.260	young	old	SMN
IPL.L	0.400	0.380		0.300	young	old	SalVentAttn
IPL.R	0.420	0.420		0.340	young	old	SalVentAttn
SMG.L	0.380	0.380		0.310	young	old	SMN
PCUN.L	0.370	0.340		0.290	young	old	DMN
PCUN.R	0.390	0.360		0.300	young	old	DMN
TPOsup.L	0.460	0.440		0.400	young	old	SMN
TPOsup.R	0.450	0.440		0.380	young	old	SMN
TPOmid.L	0.540	0.490		0.450	young	old	Subcortical
TPOmid.R	0.520	0.470		0.450	young	old	Subcortical
ITG.L	0.410	0.380		0.360	young	old	DMN
ITG.R	0.420	0.380		0.360	young	old	DMN
LING.L	0.250	0.230		0.300	old	middle	Visual
LING.R	0.260	0.250		0.300	old	middle	Visual
IOG.L	0.300	0.270		0.320	old	middle	Visual
IOG.R	0.320	0.320		0.380	old	young	Visual
PCL.R	0.290	0.260		0.310	old	middle	SMN
HES.L	0.370	0.390		0.440	old	young	SMN
HES.R	0.380	0.400		0.440	old	young	SMN
STG.R	0.300	0.320		0.370	old	young	SMN
Vermis7	0.350	0.340		0.400	old	middle	Visual
OLF.L	0.530	0.540		0.450	middle	old	SMN
SMG.R	0.390	0.400		0.310	middle	old	SMN
ANG.L	0.440	0.450		0.390	middle	old	SalVentAttn
ANG.R	0.420	0.430		0.350	middle	old	SalVentAttn
STG.L	0.350	0.390		0.380	middle	young	SMN

Table A.1 (continued)

Region Name	Young group mean	Network
ORBsup.L	0.427	DMN
ORBsup.R	0.431	DMN
ORBsupmed.L	0.502	DMN
ORBsupmed.R	0.460	DMN
REC.L	0.489	DMN
REC.R	0.470	DMN
PCG.L	0.458	DMN
ITG.L	0.412	DMN
ITG.R	0.419	DMN
IFGoperc.L	0.410	SalVentAttn
IFGtriang.L	0.409	SalVentAttn
ORBinf.L	0.455	SalVentAttn
ORBinf.R	0.432	SalVentAttn
IPL.L	0.402	SalVentAttn
IPL.R	0.424	SalVentAttn
ANG.L	0.444	SalVentAttn
ANG.R	0.420	SalVentAttn
OLF.R	0.502	SMN
TPOsup.L	0.459	SMN
TPOsup.R	0.446	SMN
OLF.L	0.529	SMN
PHG.L	0.427	Subcortical
PHG.R	0.423	Subcortical
AMYG.L	0.478	Subcortical
TPOmid.L	0.537	Subcortical
TPOmid.R	0.522	Subcortical

Table A.2: Nodes with High Flexibility in the Young Age Group. The nodes in the young age group that show a significant difference (p < 0.05) in flexibility scores(F) across age groups with F > 0 = 0.4

<b>Region Name</b>	Middle group mean	Network
ORBsup.L	0.411	DMN
ORBsup.R	0.424	DMN
ORBsupmed.L	0.488	DMN
ORBsupmed.R	0.431	DMN
REC.L	0.452	DMN
REC.R	0.457	DMN
PCG.L	0.455	DMN
ORBinf.L	0.410	SalVentAttn
ORBinf.R	0.401	SalVentAttn
IPL.R	0.417	SalVentAttn
ANG.L	0.451	SalVentAttn
ANG.R	0.433	SalVentAttn
OLF.R	0.493	SMN
TPOsup.L	0.436	SMN
TPOsup.R	0.437	SMN
OLF.L	0.542	SMN
AMYG.L	0.462	Subcortical
TPOmid.L	0.486	Subcortical
TPOmid.R	0.472	Subcortical

Table A.3: Nodes with High Flexibility in the Middle Age Group. The nodes in the middle age group that show a significant difference (p < 0.05) in flexibility scores(F) across age groups with F > 0.4

<b>Region Name</b>	Old group mean	Network
ORBsupmed.L	0.445	DMN
REC.L	0.427	DMN
REC.R	0.407	DMN
PCG.L	0.404	DMN
OLF.R	0.422	SMN
TPOsup.L	0.400	SMN
HES.L	0.436	SMN
HES.R	0.436	SMN
OLF.L	0.447	SMN
AMYG.L	0.425	Subcortical
TPOmid.L	0.450	Subcortical
TPOmid.R	0.450	Subcortical

Table A.4: Nodes with High Flexibility in the Old Age Group. The nodes in the old age group that show a significant difference (p < 0.05) in flexibility scores(F) across age groups with F > 0.4

Table A.5: Brain Regions with Significant Differences in Participation Coefficient across Age Groups. This table displays the brain regions that exhibited a significant difference (p<0.05) in participation coefficient values among the young, middle, and old age groups. The mean and standard deviation values for each age group are provided for these regions. These findings highlight the varying levels of information integration across different brain regions in relation to age.

Region Names	Network	Young -	Middle	Old -	Young-	Middle-	Old-
		mean	- mean	mean	StdDev	StdDev	StdDev
Frontal-Sup-Orb-L	DMN	0.717	0.693	0.652	0.196	0.221	0.233
Frontal-Inf-Orb-R	SalVentAttn	0.710	0.716	0.752	0.167	0.179	0.170
Lingual-L	Visual	0.644	0.627	0.688	0.215	0.202	0.190
Lingual-R	Visual	0.658	0.625	0.678	0.214	0.201	0.189
Occipital-Inf-L	Visual	0.656	0.635	0.683	0.214	0.206	0.200
Occipital-Inf-R	Visual	0.645	0.638	0.693	0.218	0.216	0.191
Paracentral-Lobule-R	SMN	0.652	0.628	0.693	0.197	0.203	0.193
Heschl-L	SMN	0.642	0.668	0.699	0.213	0.208	0.201
Heschl-R	SMN	0.611	0.657	0.683	0.225	0.212	0.204
Temporal-Sup-L	SMN	0.680	0.722	0.742	0.195	0.172	0.172
Temporal-Sup-R	SMN	0.674	0.720	0.748	0.190	0.166	0.161
Temporal-Inf-L	DMN	0.719	0.721	0.635	0.182	0.188	0.236
Temporal-Inf-R	DMN	0.755	0.743	0.695	0.151	0.165	0.213
Cerebelum-8-L	Subcortical	0.644	0.610	0.589	0.184	0.204	0.224

Table A.6: Brain Regions with Significant Differences in Within-Module Degree z-score across Age Groups. Regions that show a significant difference (p<0.05) across age groups in their within-module degree scores. The table shown is a long table that provides the regions that show a significant difference across age groups in their within-module degree scores. The table includes columns for the region names, network, mean degree scores, and standard deviations for each age group. The within-module degree scores for each region are negative or positive, indicating the degree to which the region interacts with other regions within the same module.

<b>Region Names</b>	Network	Young -	Middle	Old -	Young-	Middle-	Old-
		mean	- mean	mean	StdDev	StdDev	StdDev
Frontal-Inf-Oper-L	SalVentAttn	-0.220	-0.134	0.043	0.649	0.758	0.720
Frontal-Inf-Oper-R	SalVentAttn	-0.117	0.070	0.177	0.738	0.716	0.685
Frontal-Inf-Tri-R	SalVentAttn	0.210	0.359	0.356	0.652	0.685	0.652
Frontal-Inf-Orb-R	SalVentAttn	0.166	0.283	0.106	0.758	0.640	0.728
Cingulum-Post-L	DMN	-0.565	-0.586	-0.737	0.795	0.766	0.793
ParaHippocampal-L	Subcortical	-0.023	0.213	0.437	0.846	0.868	0.789
ParaHippocampal-R	Subcortical	-0.008	0.190	0.566	0.839	0.797	0.724
Lingual-L	Visual	0.627	0.588	0.274	0.566	0.549	0.673
Lingual-R	Visual	0.670	0.562	0.302	0.451	0.596	0.646
Occipital-Inf-L	Visual	0.117	0.194	-0.156	0.690	0.767	0.927
Occipital-Inf-R	Visual	-0.015	-0.091	-0.320	0.726	0.768	1.002
Parietal-Inf-L	SalVentAttn	-0.273	-0.250	0.010	0.652	0.713	0.675
Parietal-Inf-R	SalVentAttn	-0.611	-0.634	-0.310	0.741	0.806	0.841
SupraMarginal-R	SMN	-0.399	-0.467	-0.138	0.820	0.867	0.825
Angular-R	SalVentAttn	-0.564	-0.696	-0.496	0.844	0.806	0.796
Paracentral-Lobule-R	SMN	-0.049	0.038	-0.373	0.648	0.715	0.832
Heschl-R	SMN	-0.810	-0.695	-0.541	1.053	0.963	0.916
Temporal-Sup-R	SMN	0.483	0.298	0.349	0.714	0.785	0.735
Cerebelum-3-L	Subcortical	-1.349	-0.904	-0.777	1.045	0.982	0.977
Cerebelum-3-R	Subcortical	-1.340	-1.028	-0.764	0.969	0.944	0.954
Cerebelum-8-L	Subcortical	0.688	0.637	0.475	0.548	0.733	0.746

Table A.7: Brain Regions with Significant Difference in Both Participation Coefficient and Within-Module Degree z-score across Age Groups. Regions showing a significant difference (p<0.05) across age groups in their within-module degree scores and the corresponding participation coefficient. The table consists of the columns: Region Names, Network, Young-WMD, Young-PC, Middle-WMD, Middle-PC, Old-WMD, and Old-PC. The Region Names and Network columns show the names of the brain regions and the corresponding functional network they belong to, respectively. The Young-WMD, Middle-WMD, and Old-WMD columns show the within-module degree scores of each region for young, middle-aged, and older participants, respectively. The Young-PC, Middle-PC, and Old-PC columns show the participation coefficients of each region for young, middle-aged, and older participants, respectively.

<b>Region Names</b>	Network	Young -	Young	Middle	Middle	Old -	Old
		WMD	- PC	- WMD	- PC	WMD	- PC
			Mean :		Mean :		Mean :
			$0.673 \pm$		$0.672 \pm$		$0.675 \pm$
			0.047		0.045		0.043
Frontal-Inf-Oper-L	SalVentAttn	-0.220	0.671	-0.134	0.680	0.043	0.676
Frontal-Inf-Oper-R	SalVentAttn	-0.117	0.676	0.070	0.680	0.177	0.693
Frontal-Inf-Tri-R	SalVentAttn	0.210	0.698	0.359	0.685	0.356	0.719
Frontal-Inf-Orb-R	SalVentAttn	0.166	0.710	0.283	0.716	0.106	0.752
Cingulum-Post-L	DMN	-0.565	0.721	-0.586	0.718	-0.737	0.704
ParaHippocampal-L	Subcortical	-0.023	0.668	0.213	0.666	0.437	0.671
ParaHippocampal-R	Subcortical	-0.008	0.688	0.190	0.695	0.566	0.671
Lingual-L	Visual	0.627	0.644	0.588	0.627	0.274	0.688
Lingual-R	Visual	0.670	0.658	0.562	0.625	0.302	0.678
Occipital-Inf-L	Visual	0.117	0.656	0.194	0.635	-0.156	0.683
Occipital-Inf-R	Visual	-0.015	0.645	-0.091	0.638	-0.320	0.693
Parietal-Inf-L	SalVentAttn	-0.273	0.704	-0.250	0.693	0.010	0.679
Parietal-Inf-R	SalVentAttn	-0.611	0.699	-0.634	0.686	-0.310	0.689
SupraMarginal-R	SMN	-0.399	0.670	-0.467	0.683	-0.138	0.686
Angular-R	SalVentAttn	-0.564	0.698	-0.696	0.704	-0.496	0.705
Paracentral-Lobule-R	SMN	-0.049	0.652	0.038	0.628	-0.373	0.693
Heschl-R	SMN	-0.810	0.611	-0.695	0.657	-0.541	0.683
Temporal-Sup-R	SMN	0.483	0.674	0.298	0.720	0.349	0.748
Cerebelum-3-L	Subcortical	-1.349	0.628	-0.904	0.644	-0.777	0.634
Cerebelum-3-R	Subcortical	-1.340	0.608	-1.028	0.623	-0.764	0.634
Cerebelum-8-L	Subcortical	0.688	0.644	0.637	0.610	0.475	0.589

Table A.8: Identification of Connector Hubs in the Network. Nodes labeled as '1' in this table represent connector hubs, characterized by high participation coefficient values. Connector hubs are indicative of strong integration and information exchange across different brain regions in the network. Nodes labeled as '0' do not meet the criteria for connector hubs. This classification provides insights into the network's architecture and its capacity for information integration.

Region names	Network	Young	Middle	Old
'Frontal-Inf-Oper-L	'SalVentAttn	0	0	1
'Frontal-Inf-Oper-R	'SalVentAttn	0	1	1
'Frontal-Inf-Tri-R	'SalVentAttn	1	1	1
'Frontal-Inf-Orb-R	'SalVentAttn	1	1	1
'Rolandic-Oper-R	'SMN	0	1	0
'Hippocampus-R	'Subcortical	1	1	1
'ParaHippocampal-R	'Subcortical	0	1	0
'Lingual-L	'Visual	0	0	1
'Lingual-R	'Visual	0	0	1
'Parietal-Inf-L	'SalVentAttn	0	0	1
'Putamen-R	'Subcortical	0	0	1
'Thalamus-L	'Subcortical	0	0	1
'Thalamus-R	'Subcortical	0	0	1
'Temporal-Sup-R	'SMN	1	1	1
'Temporal-Mid-L	'DMN	1	1	0
'Temporal-Mid-R	'DMN	1	1	1

Table A.9: Identification of Provincial Hubs in the Network. Nodes labelled as '1' in this table represent provincial hubs, characterized by high within-module degree values and low participation coefficient values. Provincial hubs indicate specialized regions that primarily interact within their own modules. Nodes labelled as '0' do not meet the criteria for provincial hubs. This classification provides insights into the network's organization, with nodes serving as specialized provincial hubs within their respective modules.

Region names	Network	Young	Middle	Old
'Rolandic-Oper-L	'SMN	1	0	0
'Rolandic-Oper-R	'SMN	1	0	0
'ParaHippocampal-L	'Subcortical	0	1	1
'ParaHippocampal-R	'Subcortical	0	0	1
'Lingual-L	'Visual	1	1	0
'Lingual-R	'Visual	1	1	0
'Occipital-Sup-L	'Visual	1	1	1
'Occipital-Sup-R	'Visual	1	1	1
'Occipital-Mid-L	'Visual	1	1	1
'Occipital-Inf-L	'Visual	1	1	0
'Paracentral-Lobule-L	'SMN	0	1	0
'Paracentral-Lobule-R	'SMN	0	1	0
'Thalamus-L	'Subcortical	1	0	0
'Thalamus-R	'Subcortical	1	0	0
'Cerebelum-8-L	'Subcortical	1	1	1
'Cerebelum-8-R	'Subcortical	1	1	1
'Cerebelum-9-L	'Subcortical	1	1	1
'Cerebelum-9-R	'Subcortical	1	1	1
'Vermis-6	'Visual	1	1	0



Figure A.1: Within-Module Degree and Participation Coefficients of Nodes with Significant Age-Related Differences in WMD Scores. Subfigures (a, c, e) depict the within-module degree z-scores, while subfigures (b, d, f) show the participation coefficients, color-coded to represent positive (red) and negative (blue) WMD scores. Nodes above the mean PC are considered to have high Participation Coefficients.



(a) Young age group. Legend: A.2

BrainNet Visualization of nodes that show age effect and are significantly different across age groups.



(b) Middle age group. Legend: A.3

BrainNet Visualization of nodes that show age effect and are significantly different across age groups.



(c) Old age group. Legend: A.4

Figure A.2: Nodes whose flexibilities show a significant age effect and differences across age groups (p < 0.05). The labelled nodes are those that show the highest flexibilities > 0.4. The regions and their information corresponding to the groups they showed the highest flexibility in can be found in A.2,A.3,A.4



Young, Middle and Old mean participation coefficient

Figure A.3: Brain Regions with Significant Differences in Participation Coefficients across Age Groups. This figure displays brain regions that exhibited a statistically significant difference in participation coefficients among the different age groups. For further details on the specific brain regions and corresponding statistical analysis, refer to A.5

## TASKS

Table A.10: Correlation of Nodal Flexibility with Benton (Visual Perception and Memory) and Cattell (Fluid Intelligence) Task Scores. Regions that show a significant correlation of nodal flexibility and task scores of Benton (Visual perception and memory) and Cattell (fluid intelligence). Flexibility captures the dynamic nature of brain connectivity and reflects the ability of brain regions to adapt and reconfigure their network relationships over time. Negative and positive correlations indicate the direction and strength of the relationship, respectively.

ROI	Network	Correlation	Benton(1)/Cattelll(2)
Frontal-Inf-Oper-L	SalVentAttn	0.090	1
Frontal-Inf-Orb-L	SalVentAttn	0.103	1
Frontal-Inf-Orb-R	SalVentAttn	0.092	1
Olfactory-L	SMN	0.114	1
Olfactory-R	SMN	0.130	1
Frontal-Med-Orb-L	DMN	0.091	1
Rectus-R	DMN	0.080	1
Cingulum-Post-L	DMN	0.121	1
ParaHippocampal-L	Subcortical	0.096	1
Lingual-L	Visual	-0.160	1
Lingual-R	Visual	-0.105	1
Occipital-Inf-R	Visual	-0.149	1
Parietal-Inf-L	SalVentAttn	0.090	1
Parietal-Inf-R	SalVentAttn	0.109	1
SupraMarginal-R	SMN	0.121	1
Angular-R	SalVentAttn	0.165	1
Precuneus-L	DMN	0.096	1
Precuneus-R	DMN	0.095	1
Temporal-Sup-R	SMN	-0.082	1
Temporal-Pole-Sup-R	SMN	0.102	1
Temporal-Inf-L	DMN	0.088	1
Frontal-Sup-Orb-L	DMN	0.086	2
Frontal-Sup-Orb-R	DMN	0.124	2
Frontal-Mid-L	SalVentAttn	0.086	2
Frontal-Mid-R	SalVentAttn	0.105	2
Frontal-Inf-Oper-L	SalVentAttn	0.192	2
ROI	Network	Correlation	Benton(1)/Cattelll(2)
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Frontal-Inf-Tri-L	SalVentAttn	0.154	2
Frontal-Inf-Orb-L	SalVentAttn	0.115	2
Supp-Motor-Area-R	SMN	0.080	2
Olfactory-L	SMN	0.216	2
Olfactory-R	SMN	0.184	2
Frontal-Med-Orb-L	DMN	0.119	2
Frontal-Med-Orb-R	DMN	0.134	2
Rectus-R	DMN	0.150	2
Cingulum-Mid-L	Subcortical	0.181	2
Cingulum-Mid-R	Subcortical	0.141	2
Cingulum-Post-L	DMN	0.113	2
ParaHippocampal-L	Subcortical	0.137	2
ParaHippocampal-R	Subcortical	0.106	2
Amygdala-L	Subcortical	0.082	2
Lingual-L	Visual	-0.164	2
Lingual-R	Visual	-0.115	2
Occipital-Inf-L	Visual	-0.098	2
Occipital-Inf-R	Visual	-0.157	2
Parietal-Inf-L	SalVentAttn	0.170	2
Parietal-Inf-R	SalVentAttn	0.222	2
SupraMarginal-L	SMN	0.179	2
SupraMarginal-R	SMN	0.256	2
Angular-L	SalVentAttn	0.171	2
Angular-R	SalVentAttn	0.209	2
Precuneus-L	DMN	0.174	2
Precuneus-R	DMN	0.172	2
Paracentral-Lobule-R	SMN	-0.137	2
Temporal-Sup-R	SMN	-0.115	2
Temporal-Pole-Sup-L	SMN	0.115	2
Temporal-Pole-Sup-R	SMN	0.155	2
Temporal-Mid-R	DMN	-0.091	2
Temporal-Pole-Mid-L	Subcortical	0.088	2
Temporal-Pole-Mid-R	Subcortical	0.104	2
Temporal-Inf-L	DMN	0.115	2

Table A.10 (continued)

Table A.10 (continued)

ROI	Network	Correlation	Benton(1)/Cattelll(2)
Temporal-Inf-R	DMN	0.176	2
Cerebelum-Crus1-L	DMN	-0.087	2
Cerebelum-Crus1-R	DMN	-0.107	2
Vermis-7	Visual	-0.110	2

Table A.11: Correlation of Participation Coefficient with Benton (Visual Perception and Memory) and Cattell (Fluid Intelligence) Task Scores. Regions that show a significant correlation of participationcoefficient and task scores of Benton (Visual perception and memory) and Cattell (fluid intelligence). The participation coefficient measures the degree to which a region connects with different network modules. Negative and positive correlations indicate the direction and strength of the relationship, respectively.

ROI	Network	Correlation	Benton(1)/Cattelll(2)
Olfactory-R	SMN	0.100	1
Cingulum-Mid-L	Subcortical	0.081	1
Fusiform-L *	Visual	0.081	1
Precuneus-R	DMN	0.080	1
Caudate-R	Subcortical	-0.091	1
Temporal-Inf-L	DMN	0.125	1
Temporal-Inf-R	DMN	0.149	1
Vermis-10	Visual	-0.114	1
Frontal-Sup-L	DMN	0.099	2
Frontal-Inf-Oper-L	SalVentAttn	-0.135	2
Frontal-Inf-Oper-R	SalVentAttn	-0.159	2
Frontal-Inf-Tri-L	SalVentAttn	-0.092	2
Frontal-Inf-Orb-L	SalVentAttn	0.100	2
Frontal-Inf-Orb-R	SalVentAttn	0.131	2
Rolandic-Oper-L	SMN	0.269	2
Rolandic-Oper-R	SMN	0.270	2
Rectus-L	DMN	0.090	2
Cingulum-Post-R	DMN	0.120	2
Hippocampus-R	Subcortical	-0.164	2
ParaHippocampal-L	Subcortical	-0.162	2
ParaHippocampal-R	Subcortical	-0.218	2
Lingual-L	Visual	0.244	2
Lingual-R	Visual	0.222	2
Occipital-Sup-L	Visual	0.106	2
Occipital-Sup-R	Visual	0.086	2
Occipital-Mid-L	Visual	0.149	2
Occipital-Mid-R	Visual	0.095	2
Occipital-Inf-L	Visual	0.201	2
Occipital-Inf-R	Visual	0.122	2

ROI	Network	Correlation	Benton(1)/Cattelll(2)
Parietal-Inf-L	SalVentAttn	-0.181	2
Parietal-Inf-R	SalVentAttn	-0.185	2
SupraMarginal-R	SMN	-0.196	2
Angular-R	SalVentAttn	-0.108	2
Paracentral-Lobule-L	SMN	0.087	2
Paracentral-Lobule-R	SMN	0.182	2
Caudate-L	Subcortical	-0.085	2
Caudate-R	Subcortical	-0.089	2
Putamen-L	Subcortical	-0.097	2
Putamen-R	Subcortical	-0.123	2
Thalamus-L	Subcortical	-0.091	2
Temporal-Mid-L	DMN	0.109	2
Temporal-Mid-R	DMN	0.095	2
Cerebelum-3-L	Subcortical	-0.190	2
Cerebelum-3-R	Subcortical	-0.203	2
Cerebelum-7b-L	SMN	0.130	2
Cerebelum-8-L	Subcortical	0.137	2
Cerebelum-8-R	Subcortical	0.126	2
Vermis-3	Visual	-0.119	2
Vermis-4-5	Visual	-0.082	2
Vermis-8	Visual	0.081	2
Vermis-10	Visual	-0.181	2

Table A.11 (continued)

Table A.12: Correlation of Within-Module Degree z-score with Benton (Visual Perception and Memory) and Cattell (Fluid Intelligence) Task Scores. Regions that show a significant correlation of withinmodule degree and task scores of Benton (Visual perception and memory) and Cattell (fluid intelligence). The within-module degree measures the connectivity of a region within its respective network module. Negative and positive correlations indicate the direction and strength of the relationship, respectively.

ROI	Network	Correlation	Benton(1)/Cattelll(2)
Frontal-Inf-Oper-L	SalVentAttn	-0.123	1
Frontal-Inf-Oper-R	SalVentAttn	-0.081	1
Rolandic-Oper-L	SMN	0.147	1
Rolandic-Oper-R	SMN	0.084	1
Cingulum-Mid-L	Subcortical	0.090	1
Cingulum-Mid-R	Subcortical	0.095	1
ParaHippocampal-L	Subcortical	-0.134	1
ParaHippocampal-R	Subcortical	-0.159	1
Cuneus-L	Visual	-0.080	1
Lingual-L	Visual	0.163	1
Lingual-R	Visual	0.191	1
Occipital-Mid-L	Visual	0.082	1
Occipital-Inf-L	Visual	0.129	1
Parietal-Inf-R	SalVentAttn	-0.087	1
Angular-R	SalVentAttn	-0.132	1
Paracentral-Lobule-L	SMN	0.093	1
Paracentral-Lobule-R	SMN	0.121	1
Thalamus-L	Subcortical	-0.109	1
Heschl-R	SMN	-0.081	1
Temporal-Mid-L	DMN	0.119	1
Temporal-Mid-R	DMN	0.117	1
Cerebelum-3-L	Subcortical	-0.118	1
Cerebelum-3-R	Subcortical	-0.164	1
Cerebelum-8-L	Subcortical	0.088	1
Cerebelum-9-L	Subcortical	0.106	1
Cerebelum-9-R	Subcortical	0.136	1
Vermis-10	Visual	-0.112	1
Precentral-L	SalVentAttn	0.117	2
Frontal-Sup-L	DMN	0.143	2

ROI	Network	Correlation	Benton(1)/Cattelll(2)
Frontal-Sup-R	DMN	0.099	2
Frontal-Sup-Orb-L	DMN	0.126	2
Frontal-Sup-Orb-R	DMN	0.084	2
Frontal-Mid-L	SalVentAttn	0.149	2
Frontal-Mid-R	SalVentAttn	0.084	2
Frontal-Inf-Orb-R	SalVentAttn	-0.091	2
Supp-Motor-Area-L	SMN	0.087	2
Olfactory-L	SMN	0.095	2
Olfactory-R	SMN	0.109	2
Frontal-Sup-Medial-L	DMN	0.102	2
Frontal-Sup-Medial-R	DMN	0.080	2
Cingulum-Mid-L	Subcortical	0.114	2
Cingulum-Mid-R	Subcortical	0.091	2
ParaHippocampal-R	Subcortical	0.089	2
Amygdala-R	Subcortical	0.118	2
Fusiform-L	Visual	0.093	2
Fusiform-R	Visual	0.094	2
Parietal-Inf-L	SalVentAttn	0.100	2
Precuneus-L	DMN	0.094	2
Putamen-R	Subcortical	-0.089	2
Heschl-R	SMN	-0.085	2
Temporal-Sup-R	SMN	-0.101	2
Temporal-Pole-Sup-L	SMN	0.111	2
Temporal-Inf-L	DMN	0.197	2
Temporal-Inf-R	DMN	0.162	2
Cerebelum-6-L	SMN	0.085	2
Vermis-9	Visual	-0.084	2
Vermis-10	Visual	-0.124	2

Table A.12 (continued)

Table A.13: Connector Hubs: Correlation of Participation Coefficient and Within-Module Degree zscore with Benton and Cattell Task Scores. Connector hubs are identified with the PC and WMD scores (high PC). Correlation values of both measures with Benton and Cattell task scores are also captured. Considering age to be a continuous variable, column 'corr-with-task' captures the PC/WMD with the Benton/Cattell task. Cattell task has been greyed out for better readability. The numbers under the columns 'young,'middle and 'old denote whether the region is a connector hub in the respective age group.

ROI	Region names	Network	Young	Middle	Old	Corr	Benton(1	) WMD(1)
						with	/ Cat-	/ PC(2)
						task	tell(2)	
8	Frontal-Mid-R	SalVentAttn	1	1	1	0.084	2	2
11	Frontal-Inf-Oper-L	SalVentAttn	0	0	1	-0.123	1	1
12	Frontal-Inf-Oper-R	SalVentAttn	0	1	1	-0.081	1	1
16	Frontal-Inf-Orb-R	SalVentAttn	1	1	1	0.131	2	1
16	Frontal-Inf-Orb-R	SalVentAttn	1	1	1	-0.091	2	2
18	Rolandic-Oper-R	SMN	0	1	0	0.084	1	1
38	Hippocampus-R	Subcortical	1	1	1	-0.164	2	1
40	ParaHippocampal-R	Subcortical	0	1	0	-0.159	1	1
40	ParaHippocampal-R	Subcortical	0	1	0	0.089	2	2
47	Lingual-L	Visual	0	0	1	0.163	1	1
48	Lingual-R	Visual	0	0	1	0.191	1	1
61	Parietal-Inf-L	SalVentAttn	0	0	1	-0.181	2	1
61	Parietal-Inf-L	SalVentAttn	0	0	1	0.100	2	2
74	Putamen-R	Subcortical	0	0	1	-0.123	2	1
74	Putamen-R	Subcortical	0	0	1	-0.089	2	2
77	Thalamus-L	Subcortical	0	0	1	-0.109	1	1
82	Temporal-Sup-R	SMN	1	1	1	-0.101	2	2
85	Temporal-Mid-L	DMN	1	1	0	0.119	1	1
86	Temporal-Mid-R	DMN	1	1	1	0.117	1	1

Table A.14: Provincial Hubs: Correlation of Participation Coefficient and Within-Module Degree zscore with Benton and Cattell Task Scores. Provincial hubs are identified with the PC and WMD scores (low PC and high WMD). Correlation values of both measures with Benton and Cattell task scores are also captured. Considering age to be a continuous variable, column 'corr-with-task' captures the PC/WMD with the Benton/Cattell task. Cattell task has been greyed out for better readability. The numbers under the columns 'young, 'middle and 'old denote whether the region is a provincial hub in the respective age group.

ROI	<b>Region names</b>	Network	Young	Middle	Old	Corr	Benton(1	) WMD(1)
						with	/ Cat-	/ PC(2)
						task	tell(2)	
17	Rolandic-Oper-L	SMN	1	0	0	0.147	1	1
18	Rolandic-Oper-R	SMN	1	0	0	0.084	1	1
39	ParaHippocampal-L	Subcortical	0	1	1	-0.134	1	1
40	ParaHippocampal-R	Subcortical	0	0	1	-0.159	1	1
40	ParaHippocampal-R	Subcortical	0	0	1	0.089	2	2
47	Lingual-L	Visual	1	1	0	0.163	1	1
48	Lingual-R	Visual	1	1	0	0.191	1	1
49	Occipital-Sup-L	Visual	1	1	1	0.106	2	1
50	Occipital-Sup-R	Visual	1	1	1	0.086	2	1
51	Occipital-Mid-L	Visual	1	1	1	0.082	1	1
53	Occipital-Inf-L	Visual	1	1	0	0.129	1	1
69	Paracentral-Lobule-L	SMN	0	1	0	0.093	1	1
70	Paracentral-Lobule-R	SMN	0	1	0	0.121	1	1
77	Thalamus-L	Subcortical	1	0	0	-0.109	1	1
103	Cerebelum-8-L	Subcortical	1	1	1	0.088	1	1
104	Cerebelum-8-R	Subcortical	1	1	1	0.126	2	1
105	Cerebelum-9-L	Subcortical	1	1	1	0.106	1	1
106	Cerebelum-9-R	Subcortical	1	1	1	0.136	1	1

## **Related Publications**

- Arpita Dash, Bapi S. Raju, Dipanjan Roy, and P. K. Vinod. "Characterizing the Dynamic Reorganization in Healthy Ageing and Classification of Brain Age." In 2022 International Joint Conference on Neural Networks (IJCNN), pp. 1-7. IEEE, 2022. Accepted as a full paper. [147]
- Arpita Dash, Bapi S. Raju, Dipanjan Roy and P. K. Vinod, "Characterizing Age-Related Functional Changes and their Association with Cognitive Performance: A Graph Theory Approach", (under submission)

## **Other Publications**

 Oota, Subba Reddy, Archi Yadav, Arpita Dash, Bapi S. Raju, and Avinash Sharma. "Multiple GraphHeat Networks for Structural to Functional Brain Mapping." In 2022 International Joint Conference on Neural Networks (IJCNN), pp. 1-8. IEEE, 2022.

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