

INVESTIGATING BRAIN GENDER-BASED
DIMORPHISM AND COGNITIVE NEUROANATOMICAL
VARIATIONS IN HUFFAZ AND NON-HUFFAZ USING
MAGNETIC RESONANCE IMAGING AND ARTIFICIAL
INTELLIGENCE

BY

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ABSTRACT

This doctoral research examines how intensive cognitive training influences sexual dimorphism in brain structure, focusing on Huffaz—individuals who have memorized the entire Quran. Huffaz undergo sustained cognitive training, which may stimulate neuroplasticity and induce structural changes in the brain. This study addresses a critical gap in understanding how such culturally specific training modulates sex differences in brain morphology. Using voxel-based morphometry (VBM), voxel of interest (VOI) analyses, and machine learning classification, this study explores the interaction between cognitive training and biological sex. The primary objectives were to: (1) analyse sex differences in brain structure and assess the effects of Huffaz training using VBM, (2) investigate sexually dimorphic brain regions through VOI analysis with volume estimation and fractal analysis, and (3) develop machine learning models to classify sex based on brain structure while evaluating the impact of Huffaz training. A retrospective dataset of T1-weighted MRI scans from 47 healthy young adults (19 males, 28 females; aged 20-25) was used, including 23 Huffaz and 24 non-Huffaz. Both VBM and VOI analyses were applied across multiple brain atlases. Machine learning models—logistic regression, support vector machines, deep learning, and random forest—were trained to classify sex based on brain structure. VBM analysis revealed significant sexual dimorphism, with males exhibiting larger grey matter volumes in the cerebellum, fusiform gyrus, and temporal gyrus. After accounting for Huffaz status, additional regions such as the hypothalamus and amygdala were identified. VOI analysis confirmed larger male brain volumes, with the medial frontal gyrus reaching significance after controlling for Huffaz training. Fractal dimension analyses highlighted structural complexity variations, with males showing higher FDs in regions like the fusiform gyrus and superior occipital gyrus, while females exhibited higher values in the parahippocampal gyrus and anterior cingulate. Machine learning models demonstrated high accuracy in sex classification, with deep learning and random forest models achieving up to 92.86% accuracy when incorporating Huffaz status. These findings underscore the potential of AI in analysing complex brain structures and integrating cultural factors into sex classification models. This study enhances our understanding of how intensive cognitive training influences brain structure and sexual dimorphism. It provides insights into the interaction between sex and culture in shaping brain plasticity, with implications for the development of sex-specific cognitive training programmes and therapeutic interventions.

ملخص البحث

تتناول هذه الدراسة الدكتوراه كيفية تأثير التدريب المعرفي المكثف على التباين الجنسي في هيكل الدماغ، مع التركيز على الحافظين (الحفاظ) الذين قاموا بحفظ القرآن الكريم كاملاً. يخضع الحافظون لتدريب معرفي مستمر، مما قد يحفز التكيف العصبي ويؤدي إلى تغييرات هيكلية في الدماغ. تعالج هذه الدراسة فجوة هامة في فهم كيفية تعديل هذا التدريب الثقافي، (VOI) وتحليل فوكسيل الاهتمام، (VBM) الفروق الجنسية في مورفولوجيا الدماغ. باستخدام تحليل موجه الفوكسيل وتقنيات التصنيف باستخدام التعلم الآلي، تستكشف هذه الدراسة التفاعل بين التدريب المعرفي والجنس البيولوجي. كانت (2) VBM، الأهداف الرئيسية: 1) تحليل الفروق الجنسية في هيكل الدماغ وتقييم تأثيرات تدريب الحافظين باستخدام مع تقدير الحجم وتحليل الكسورية، و 3) تطوير VOI التحقيق في المناطق الدماغية ذات التباين الجنسي من خلال تحليل نماذج تعلم الآلة لتصنيف الجنس بناءً على هيكل الدماغ مع تقييم تأثير تدريب الحافظين. تم استخدام مجموعة بيانات استيعادية من 47 شاباً (صحياً) 19 ذكراً، 28 أنثى؛ تتراوح أعمارهم بين 20-25 T1 من مسح الأشعة المغناطيسية للدماغ بتقنية عبر أطلسات دماغية متعددة VOI و VBM عاملاً، بما في ذلك 23 حافظاً و 24 غير حافظ. تم تطبيق كل من تحليل تم تدريب نماذج التعلم الآلي—الانحدار اللوجستي، وآلات الدعم الشعاعي، والتعلم العميق، والغابات العشوائية—لتصنيف تبايناً جنسياً ملحوظاً، حيث أظهر الذكور حجماً أكبر من المادة VBM الجنس بناءً على هيكل الدماغ. أظهر تحليل الرمادية في المخيخ والتلافيف الجدارية العليا والجدارية الصدغية. بعد أخذ حالة الحفظ في الاعتبار، تم تحديد مناطق إضافية حجم دماغ أكبر للذكور، مع الوصول إلى أهمية التلافيف الجدارية الأمامية بعد السيطرة VOI مثل الوطاء واللوزة. أكد تحليل على تأثير تدريب الحافظين. سلط تحليل أبعاد الكسورية الضوء على اختلافات التعقيد الهيكلي، حيث أظهر الذكور قيماً أعلى في مناطق مثل التلافيف الجدارية العلوية والتلافيف الصدغية العلوية، بينما أظهرت الإناث قيماً أعلى في التلافيف الحُصينية الأمامية والحزام الأمامي. أظهرت نماذج التعلم الآلي دقة عالية في تصنيف الجنس، حيث حققت نماذج التعلم العميق والغابات العشوائية دقة تصل إلى 92.86% عند تضمين حالة الحفظ. تؤكد هذه النتائج على إمكانات الذكاء الاصطناعي في تحليل الهياكل الدماغية المعقدة ودمج العوامل الثقافية في نماذج تصنيف الجنس. تعزز هذه الدراسة فهمنا لكيفية تأثير

التدريب المعرفي المكثف على هيكل الدماغ والتباين الجنسي . كما تقدم رؤى حول التفاعل بين الجنس والثقافة في تشكيل مرونة الدماغ، مع تداعيات لتطوير برامج تدريب معرفي وتدخلات علاجية محددة للجنس.



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DECLARATION

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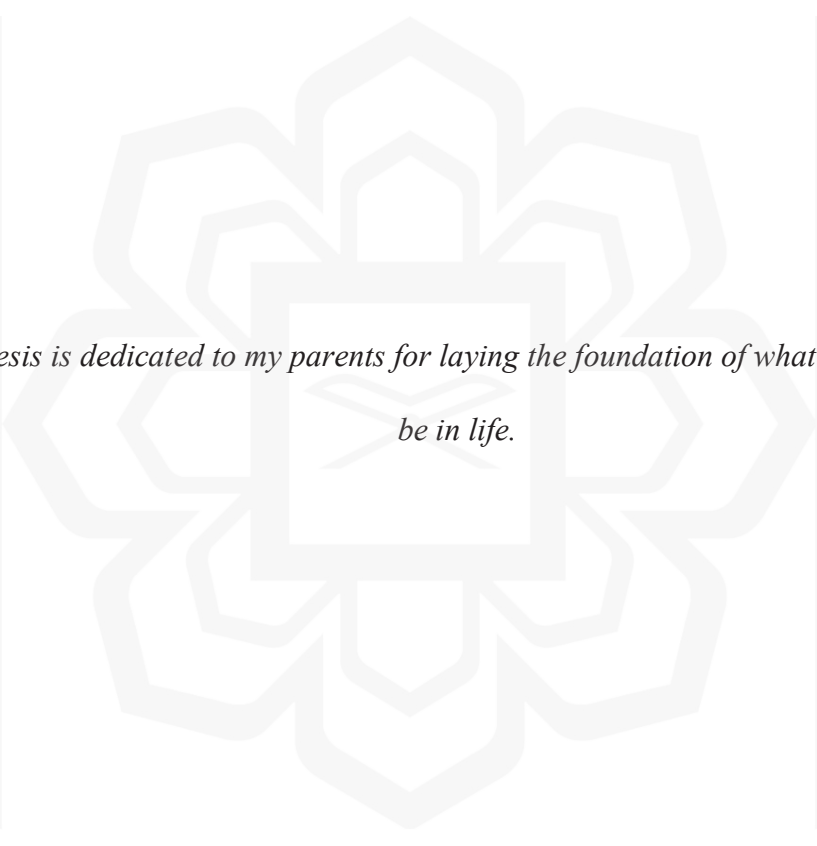
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*This thesis is dedicated to my parents for laying the foundation of what I turned out to
be in life.*

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LIST OF ABBREVIATIONS

2D	Two dimension
3D	Three dimension
AI	Artificial intelligence
ANN	Artificial Neural Networks
AUC	Area Under the Curve
CNN	Convolutional Neural Network
CoBrA	Computational Brain Anatomy Laboratory Atlas
DICOM	Digital Imaging and Communications in Medicine
FD	Fractal Dimension
FFD	Fourier Fractal Dimension
BCFD	Box Counting Fractal Dimension
GBT	Gradient Boosted Trees
GI	Gyrification Index
HSRC	Hierarchical Sparse Representation Classifier
LDA	Linear Discriminant Analysis
LPBA40	Laboratory of Neuro Imaging Probabilistic Brain Atlas
LR	Logistic Regression
MARS	Multiple Adaptive Regression Splines
MCN-ELM	Multi-Layer 3D Convolution Extreme Learning Machine
ML	Machine Learning
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
RF	Random Forests
SPM	Statistical Parametric Mapping
SulcD	Sulcal Depth
SUIT	Spatially Unbiased Atlas Template of the Cerebellum and Brainstem

SVM	Support Vector Machines
TD	Talairach Daemon
VBM	Voxel based morphometry
VOI	Voxel of interest



CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

This doctoral research study centres on sexual dimorphism in the brain, which refers to structural differences between males and females, including variations in the size, shape, and organization of specific brain regions (Sacher et al., 2013). Influenced by genetic, hormonal, and environmental factors, these differences are essential for understanding the biological basis of cognitive, emotional, and behavioural differences between sexes, contributing to our knowledge of neurodevelopment, neuropsychiatric disorders, and overall brain function (Shepherd et al., 2021).

The study of sexual brain differences, dating back to the early 20th century noting differences such as greater weight and larger circumferences in male brains compared to female brains (Janowsky, 1989). Magnetic resonance imaging (MRI) has been instrumental in enabling the study of sexual brain differences, revealing variations in size, thickness, and regional volumes between male and female brains. MRI studies revealed morphological variations between sexes (Ingallhalikar et al., 2014; Wierenga et al., 2022). While some studies highlight these differences (Lotze et al., 2019; Ritchie et al., 2018; Ruigrok et al., 2014), others emphasize their variability and potential influence of other factors beyond sex (Eliot et al., 2021; Joel et al., 2018). Artificial intelligence (AI) advancements, especially in machine learning, have further fuelled this debate, demonstrating high accuracy in classifying sex based on brain structure (Ebel et al., 2023; Sanchis-Segura et al., 2022). These technological strides highlight the growing potential of AI to provide deeper insights into complex biological patterns. This ongoing debate underscores the need

for continued research, like the present study, to employ robust methodologies and diverse perspectives. By leveraging the power of MRI and advanced AI techniques, this work can unravel the complexities of sexual brain differences and their broader implications, enhancing both scientific understanding and real-life applications.

The integration of AI technique particularly machine learning (ML) into this study is particularly relevant given its ability to uncover complex patterns in large datasets that traditional neuroimaging methods may overlook. ML techniques are well-suited for analysing structural MRI data because they can handle the high-dimensional nature of brain imaging data, identifying subtle and multidimensional patterns of brain morphology associated with sex differences and the effects of cognitive training. Unlike traditional voxel-based or region-of-interest approaches that often require predefined assumptions about brain regions of interest, ML models can explore the entire dataset simultaneously, offering an unbiased analysis of how different brain regions contribute to sexual dimorphism and neuroplastic changes. Additionally, ML can enhance the predictive power of the study by classifying brain sex with high accuracy and assessing the impact of Huffaz training as a covariate, providing a more nuanced understanding of how cognitive training interacts with biological sex to influence brain structure. By complementing traditional neuroimaging methods, ML not only broadens the scope of the analysis but also provides a robust, data-driven approach to validate and extend the findings, ultimately contributing to a more comprehensive exploration of the research questions and objectives.

Brain plasticity, the brain's ability to reorganize and adapt its structure and function in response to various stimuli, is influenced by factors like cognitive demands and new experiences (P. Li et al., 2014). This adaptability can result in structural changes, impacting memory and other cognitive functions. Studies on taxi drivers (Maguire et al., 2000), musicians (Gaser & Schlaug, 2003; Hyde et al., 2009), and individuals undergoing cognitive training (Clark et al., 2017; Metzler-Baddeley et al., 2016; Román et al., 2016) have demonstrated such plasticity, particularly in regions associated with memory and specific skills. Huffaz, or individuals who have committed the entire Quran to memory (Ariffin et al., 2015), represent a unique group engaged in intensive and prolonged

cognitive training. This practice, rooted in Islamic tradition dating back to the Prophet Muhammad's SAW era, involves rigorous memorization and continuous review of Quranic verses (Keblawi, 2014). The demanding nature of this cognitive exercise is believed to stimulate neuroplasticity, potentially leading to structural changes in the brain. The first MRI study comparing brain of Huffaz to non-Huffaz have indeed observed differences, lending support to the notion that Quran memorization can influence brain structure (Jamaludin et al., 2022). This unique group, therefore, offers valuable insights into the impact of extensive cognitive training on the brain.

In the realm of brain structural research, three methodologies—voxel-based morphometry (VBM)(Ashburner & Friston, 2000), voxel of interest (VOI) analysis(Del Mauro et al., 2022), and ML (Sanchis-Segura et al., 2022)—offer unique and complementary insights into the complexities of the brain. VBM provides a whole-brain, unbiased approach to identify subtle differences in grey matter volume between groups or across various conditions (Ashburner & Friston, 2000). VOI analysis allows for a focused examination of specific brain regions, offering detailed measurements and comparisons using metrics such as volume (Seyedi et al., 2020) and cortical complexity (fractal dimensions, FD) (Chen et al., 2023). ML, with its powerful pattern recognition capabilities, enables the classification and prediction of characteristics like sex based on brain structural features, pushing the boundaries of our understanding of individual differences. The employment of these diverse methods in brain imaging studies yields a multi-faceted understanding of brain structure, enhancing our knowledge of its intricate relationship with function and behaviour, and paving the way for advancements in neuroscience and personalized medicine.

This research seeks to address the relative lack of research investigating the complex interplay between sexual dimorphism in brain structure and the potential modulating effects of cognitive training. By focusing on the Huffaz group as a model of intensive cognitive engagement, the aim is to uncover the nuanced relationship between sex, cognitive training, and brain plasticity using a multi-pronged approach, utilizing VBM, detailed VOI analyses, and ML classification. The findings of this research have the

potential to contribute significantly to our understanding of brain plasticity, inform the development of tailored cognitive training programmes, and shed light on sex-specific considerations in educational and therapeutic interventions.

1.2 STATEMENT OF THE PROBLEM

Despite significant progress in the study of sexual dimorphism in brain structure, critical gaps remain in our understanding of how these differences are influenced by cognitive training, particularly within religiously specific contexts. While previous research has provided valuable insights into inherent biological differences between male and female brains, it has largely neglected the potential impact of intensive cognitive training practices, such as those undertaken by Huffaz, on these differences. Exploring the specific cognitive practices of Huffaz—individuals who have memorized the entire Quran through rigorous training—offers a novel opportunity to examine how such intensive, sustained cognitive activity might influence brain structure differently across sexes. This oversight limits our comprehension of the ways in which cognitive training might modify or amplify sexual dimorphism in the brain.

Moreover, the intersection of culture, cognition, and brain structure is an underexplored area in contemporary neuroscience. The influence of cultural and religious practices, specifically the rigorous memorization of the Quran by Huffaz, on brain development has not been adequately examined in relation to sexual dimorphism. Huffaz training is unique due to its combination of prolonged memorization, continuous recitation, and deep engagement with linguistic content, which provides a distinct context to explore neuroplasticity and its potential sex-specific effects. There is a lack of research addressing how such practices could lead to unique patterns of brain structure and function across sexes, thereby contributing to a more nuanced understanding of brain sexual differences.

Methodologically, the study of sexual dimorphism in relation to cognitive training benefits from the use of diverse and advanced analytical techniques, each providing complementary insights that contribute to a fuller understanding of these complex interactions. Employing VBM and VOI analysis offers detailed perspectives on structural brain differences, while ML techniques enhance the ability to classify brain sex and assess the impact of cognitive training. The integration of these methodologies enables a more nuanced exploration of how cognitive training, such as that undertaken by Huffaz, interacts with biological sex to shape brain structure and function. This multi-method approach allows for a comprehensive analysis that can identify both subtle and prominent structural differences influenced by sex and cognitive training, providing a robust framework for understanding how these factors interact.

Furthermore, this research is driven by the hypothesis that Huffaz training may modulate sexual dimorphism in the brain, with effects that vary across different brain regions and cognitive functions. Specifically, it is hypothesized that the intensive cognitive demands of Huffaz training will lead to differential neuroplastic changes in males and females, potentially enhancing or diminishing existing sexual dimorphisms in brain regions associated with memory and language processing. Investigating this hypothesis is essential to advancing our understanding of the neuroplastic changes induced by such cognitive training and how these changes may differ between sexes. By employing advanced neuroimaging techniques and ML models, the study aims to accurately classify brain sex and assess the specific impact of Huffaz training, thereby providing new insights into how cognitive training interacts with biological sex to shape brain development.

Finally, the findings from this study have the potential to inform educational practices, particularly in contexts where memorization and cognitive training are emphasized. By elucidating how such cognitive training influences brain development differently in males and females, this research could contribute to the development of tailored educational approaches that better accommodate sex-specific needs, ultimately optimizing cognitive outcomes. The implications of this research extend beyond academia,

offering insights that could shape policy and practice in educational and cognitive training settings. Understanding the effects of culturally specific cognitive training on brain structure can lead to more informed educational strategies that are sensitive to sex differences, potentially enhancing learning outcomes and cognitive development for diverse populations.

1.3 RESEARCH QUESTIONS

The works attempt to answer the following questions:

1.3.1 Primary Research Question

How does cognitive training, specifically the intensive memorization practices of Huffaz, influence sexual dimorphism in brain structure?

1.3.2 Specific Research Questions

- What are the brain volumetric differences, as measured by voxel-based morphometry and voxel of interest using multiple brain atlases, between males and females, and how does Huffaz training modulate these differences?
- Which specific brain regions exhibit sexual dimorphism when analysed using complexity measurement; box-counting and Fourier fractal dimension, and what is the impact of Huffaz training on these regions?
- Can machine learning techniques accurately classify brain sex, and how does the inclusion of Huffaz training as a covariate affect the accuracy and performance of these models?

1.4 RESEARCH OBJECTIVE

This study embarks on the following objectives:

1.4.1 General Research Objective

To investigate the influence of cognitive training, specifically the memorization practices of Huffaz, on sexual dimorphism in brain structure.

1.4.2 Specific Research Objectives

- To analyse volumetric differences in brain structure between males and females using voxel-based morphometry and voxel of interest methods and to assess the modulation effects of intensive cognitive training by Huffaz on these differences.
- To identify specific brain regions that exhibit sexual dimorphism estimated using complexity index; box-counting and Fourier fractal dimension, and to determine the impact of Huffaz training on these regions.
- To validate machine learning models to classify brain sex based on structural data and evaluate the influence of Huffaz training on the accuracy and performance of these models.

1.5 HYPOTHESIS

The study is based on the following hypotheses:

1.5.1 General Hypothesis

Cognitive training, specifically the memorization practices of Huffaz, has a significant influence on sexual dimorphism in brain structure.

1.5.2 Specific Hypotheses

- There are significant differences in brain volume between males and females as measured by voxel-based morphometry and voxel-of-interest, and these differences are modulated by the intensive cognitive training of Huffaz.
- Specific brain regions exhibit sexual dimorphism, with differences in brain complexity —estimated using box-counting fractal dimension, and Fourier fractal dimension—that are significantly impacted by Huffaz training.
- Machine learning models can accurately classify brain sex based on structural data and incorporating Huffaz training as a covariate will significantly enhance the model's accuracy and performance.

1.6 SIGNIFICANCE OF THE STUDY

The significance of this study is multifaceted, contributing to both scientific knowledge and practical applications across several fields. This study provides crucial insights into the structural differences between male and female brains, particularly in the context of cognitive training. By focusing on Huffaz, individuals who engage in intensive Quran memorization, it explores how specific religious practices may influence brain development differently in males and females. This research enhances our understanding of brain plasticity and how cognitive activities shape brain structure, contributing valuable knowledge to the field of neuroscience.

The study is significant for its innovative use of multiple analysis techniques, including volumetric analysis, FD analysis, and machine learning. By integrating these advanced methodologies, the research offers a comprehensive approach to exploring complex neurobiological phenomena. This combined methodological approach allows for a more detailed and nuanced understanding of how cognitive training impacts sexual dimorphism in the brain, providing a robust framework for identifying subtle brain differences influenced by both sex and training. The incorporation of ML models to classify brain sex and assess the impact of cognitive training underscores the growing importance of data-driven approaches in the discipline.

Understanding the impact of religious and cultural practices on brain development is another critical aspect of this study. By examining the effects of Huffaz training, the research provides insights into how specific practices can shape cognitive and neural development. These insights are particularly important in recognizing the role of culture-specific cognitive demands in brain plasticity, potentially leading to different neurodevelopmental trajectories for males and females. These findings have the potential to inform educational strategies and cognitive training programmes that are tailored to the unique needs of different populations. Moreover, the study's exploration of sex-specific effects of cognitive training could lead to more personalized educational approaches, addressing the distinct strengths and vulnerabilities of males and females.

The study also makes significant theoretical contributions by bridging the gap between biological research on sexual dimorphism and cultural studies. It offers a more comprehensive understanding of how biological and environmental factors interact to shape the human brain. By integrating insights from neuroscience, psychology, and cultural studies, this research contributes to a more holistic understanding of sex differences in cognitive and behavioural patterns. Additionally, by providing empirical evidence on how sex differences in the brain are influenced by cultural practices, the research contributes to the ongoing discourse in sex studies, particularly in understanding the biological underpinnings of sex-specific cognitive and behavioural patterns.

Finally, the findings of this study have practical implications for informing educational and cognitive training programmes, especially in contexts where religious or cultural practices are integral. The results could guide the development of policies and practices that better accommodate the cognitive diversity, ensuring that both male and female learners benefit optimally from training programmes. Furthermore, this study's findings are likely to guide future research, encouraging further exploration into the impact of specific cultural practices on brain development and cognitive function.

1.7 THEORETICAL FRAMEWORK

Figure 1.1 articulates the conceptual framework guiding the study. This framework visually represents the interrelationships between the key variables of the research: sexual dimorphism in brain structure, cognitive training (specifically Huffaz training), and brain plasticity. It provides a structured overview of how these elements interact and influence each other within the context of this study. By doing so, the framework clarifies the theoretical basis for the research and helps to illustrate the pathways through which intensive cognitive training might modulate brain morphology differently in males and females.

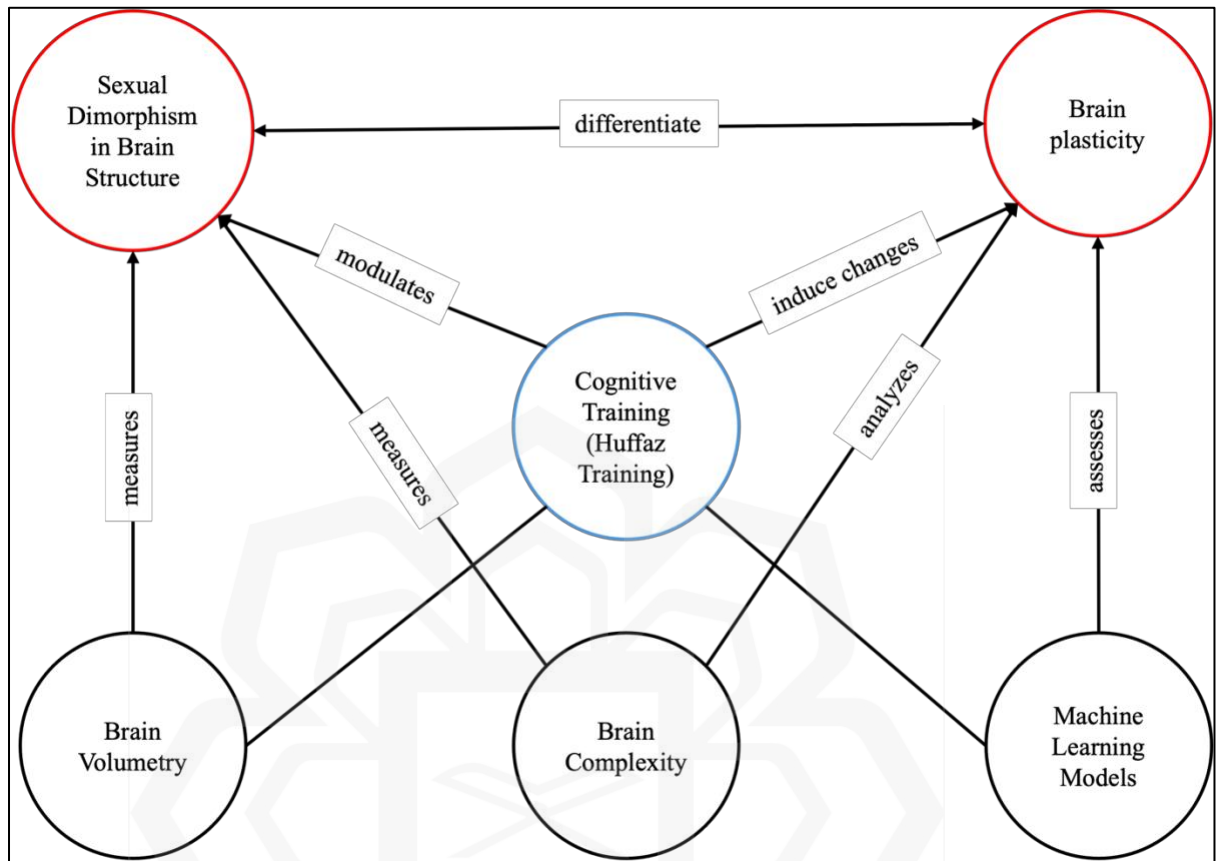


Figure 1.1 Conceptual Framework: Sexual Dimorphism, Cognitive Training, and Brain Plasticity

The conceptual framework is designed to reflect the hypothesis that cognitive training, particularly the intensive memorization practices undertaken by Huffaz, induces neuroplastic changes in the brain. These changes may not only vary by sex but also interact with inherent sexual dimorphism to produce distinct patterns of brain morphology. For instance, it is hypothesized that Huffaz training could enhance or reduce existing differences in brain structures between males and females, depending on the specific brain regions and cognitive functions involved. This framework allows the study to explore these modulating effects in a systematic manner, using a combination of VBM, voxel of interest analysis, and ML models.

Additionally, the framework illustrates the methodological approaches employed to investigate these relationships. VBM and VOI analysis provide detailed insights into regional brain differences and cortical complexity, while ML models offer a novel approach to classifying brain sex and assessing the impact of Huffaz training on these classifications. This multi-method approach not only strengthens the study's design by integrating diverse analytical techniques but also enhances the robustness of the findings by allowing for cross-validation across methods.

Overall, the conceptual framework presented in Figure 1.1 serves as a roadmap for the study, guiding the research questions, objectives, and hypotheses. It demonstrates how the study aims to fill existing gaps in the literature by examining the interplay between sex, cognitive training, and brain plasticity within a culturally specific context. By doing so, the framework underpins the study's potential to advance our understanding of how intensive cognitive training can influence brain development differently in males and females, offering new insights into the neurobiological underpinnings of cognitive and behavioural differences between sexes.

1.8 THESIS OUTLINE

This thesis is structured into six chapters, each integrating the findings of five interrelated studies that collectively address the overarching aim of examining sexual dimorphism in brain structure and the influence of intensive cognitive training, specifically within the Huffaz group. Rather than presenting each study as a standalone chapter, the thesis follows a cohesive narrative approach, where each chapter systematically synthesizes relevant materials and results from all five studies. Below is an overview of the thesis structure:

Chapter 1: Introduction

This chapter provides an overview of the research context, including the concept of sexual dimorphism in the brain and the unique cognitive training experienced by the Huffaz group. It outlines the research questions and objectives and establishes the rationale for the study. The introduction sets the stage for the investigation of how sex differences in brain structure are influenced by rigorous memorization practices, framing the core focus of the thesis.

Chapter 2: Literature Review

The literature review explores existing research on brain sexual dimorphism and neuroplasticity, focusing on structural differences between male and female brains and the effects of intensive cognitive training. This chapter synthesizes relevant studies and theories, including previous findings on VBM, VOI methods, fractal analysis, and ML approaches for brain classification. The review highlights the gaps in current research, particularly in understanding how intensive memorization, such as that undertaken by Huffaz, modulates brain structure, thus justifying the need for this study.

Chapter 3: Methodology

This chapter provides a comprehensive explanation of the research design and methodology used in this thesis. It includes detailed descriptions of the retrospective dataset, participant selection criteria, MRI acquisition protocols, and the preprocessing steps applied to the imaging data. The methodology section covers the analytical approaches used across all five studies, including volumetric analysis; VBM, VOI analysis using multiple brain atlases and complexity analysis; fractal analysis (box-counting and Fourier fractal dimension methods), and the development of ML models for sex classification based on brain structure. Each method is discussed in detail, with justifications for its application to the research objectives.

Chapter 4: Results

This chapter presents the empirical findings of the five studies conducted to address the thesis's overarching research aims. Each study investigates distinct aspects of the interplay between sexual dimorphism in brain structure and the potential modulating effects of Huffaz training.

- Study 1: Voxel-Based Morphometry Analysis

This study examines sex differences in brain structure using VBM and investigates whether these differences are modulated by Huffaz training. This approach provides a broad understanding of regional variations in sexual dimorphism, both with and without the influence of cognitive training.

- Study 2: Voxel of Interest Analysis

The second study utilizes VOI analysis to examine regional brain volume across multiple atlases. This method allows for a detailed assessment of sex-based volumetric differences and the extent to which Huffaz training influences these differences. By estimating the 3D morphological structure of specific brain regions, this study provides a comprehensive evaluation of sex-based variations in brain size and structure.

- Study 3: Box-Counting Fractal Dimension Analysis

The third study shifts focus from brain volume to structural complexity by employing box-counting fractal dimension analysis. This method quantifies the geometric complexity of brain structures, offering insights into sex differences in the organization of neural

architecture. The analysis investigates whether males and females exhibit differences in the intricate patterns of brain morphology and assesses how Huffaz training influences these complexity measures.

- Study 4: Fourier Fractal Dimension Analysis

The fourth study builds upon the previous FD analysis by using an alternative method—Fourier fractal dimension analysis—to further investigate brain complexity. This approach provides a complementary perspective, allowing for the assessment of frequency-based structural patterns in brain morphology. By comparing the results of box-counting and Fourier methods, this study offers a more nuanced understanding of how sex differences manifest in brain complexity and how cognitive training impacts these patterns.

- Study 5: Machine Learning-Based Brain Sex Classification

The final study employs ML techniques to classify brain sex based on structural data. Various brain features, including Huffaz status, are incorporated into the classification models, which are evaluated for their accuracy in predicting sex differences. This study assesses whether cognitive training enhances or diminishes the distinction between male and female brain structures, shedding light on the broader implications of neuroplasticity in sex-based classification models.

Together, these five studies provide a comprehensive, multi-dimensional exploration of the research question. Through the integration of advanced neuroimaging techniques, volumetric assessment, complexity analysis, and machine learning, this research offers a rigorous investigation of sex-based differences in brain structure and the potential modulating effects of intensive cognitive training in the Huffaz group.

Chapter 5: Discussion

This chapter provides an in-depth synthesis of the key findings from the five studies presented in Chapter 4, contextualizing them within the broader landscape of neuroscience, cognitive training, and sex-based differences in brain structure. It critically evaluates the implications of these results, comparing them with existing literature, and explores the potential underlying mechanisms driving the observed structural differences.

The first section revisits the findings of VBM and VOI analysis, interpreting the observed sex differences in brain volume and the role of Huffaz training in modulating these differences. It examines whether the volumetric patterns identified align with previous research on sexual dimorphism in the brain and discusses possible explanations for regional variations in grey matter volume. Additionally, this section explores the impact of intensive memorization training, considering the potential neuroplastic adaptations induced by repeated cognitive effort and memory retrieval in Huffaz participants.

The second section focuses on the implications of FD analysis and brain complexity measures. It discusses how variations in FD reflect underlying differences in brain structure between males and females and the extent to which cognitive training influences these geometric patterns. This section critically evaluates the potential of fractal analysis as a novel approach to studying sex-based differences in brain architecture, drawing comparisons to traditional volumetric techniques. The discussion also addresses the significance of these findings in understanding how training-related neuroplasticity affects not only the size but also the complexity of neural structures.

The third section explores the role of ML classification in distinguishing brain sex based on structural data. It examines the performance of the classification models, particularly in relation to Huffaz status, and evaluates whether cognitive training enhances or obscures the ability to predict sex differences in brain structure. This section discusses the strengths and limitations of using ML in neuroimaging research and reflects on how

classification models can contribute to understanding the broader implications of brain plasticity.

The chapter concludes by acknowledging the study's limitations, including sample size constraints, methodological challenges, and the need for longitudinal studies to assess the long-term impact of cognitive training on brain structure. It also highlights promising directions for future research, emphasizing the importance of further investigations into how different forms of cognitive training, beyond Huffaz memorization, may shape neural development and cognitive function.

Chapter 6: Conclusion

The conclusion reflects on the contribution of the research to existing knowledge on brain plasticity and sexual dimorphism and highlights the potential applications of the findings in educational and therapeutic contexts. Recommendations for future research are also provided, focusing on the long-term effects of cognitive training on brain development and the need for further investigation into sex-specific brain differences.

CHAPTER TWO

LITERATURE REVIEW

2.1 INTRODUCTION

This research focuses on sexual dimorphism in the brain, which refers to structural differences between males and females, including variations in the size, shape, and organization of specific brain regions. These differences are influenced by genetic, hormonal, and environmental factors and are fundamental to understanding the biological basis of cognitive, emotional, and behavioural variations between the sexes (Shepherd et al., 2021). Despite the progress made in understanding sex-based brain differences, the role of cognitive training in modulating these variations is still underexplored. This study seeks to bridge this gap by examining how intensive cognitive activities, such as Quran memorization in Huffaz, influence sexual dimorphism in brain structure.

Cognitive training has been shown to induce neuroplasticity, leading to structural changes in the brain. For instance, studies have demonstrated brain plasticity in response to intensive cognitive tasks such as navigation training in taxi drivers (Maguire et al., 2000) and musical training in musicians (Hyde et al., 2009). Huffaz, individuals who memorize the entire Quran through rigorous and prolonged cognitive training, provide a unique model to study the impact of sustained memory-based training on brain structure. Emerging research indicates that such training may result in structural changes in brain regions linked to memory and executive functions (Jamaludin et al., 2022).

This research employs advanced neuroimaging techniques to assess the structural differences in the brain, combining volumetric analyses such as VBM and VOI with complexity measures such as FD analysis. VBM offers an unbiased, whole-brain approach

to detect differences in grey matter volume between males and females, while VOI allows for more detailed regional analyses of specific brain structures (Ashburner & Friston, 2000). In addition to volumetric measures, complexity analyses using FD provide insights into the intricate geometric patterns and structural complexity of brain regions (Chen et al., 2023).

Moreover, this study integrates ML to investigate the predictive analysis of sexual dimorphism. ML techniques, such as classification models, enable the identification of subtle patterns in brain structure that may not be apparent through traditional statistical methods. These algorithms are particularly effective in classifying brain structure based on sex and cognitive training, providing a robust tool for analysing the impact of Huffaz training on brain morphology (Sanchis-Segura et al., 2022).

This chapter will review the existing literature on sexual dimorphism in brain structure, the effects of cognitive training on neuroplasticity, and the application of volumetric, complexity, and ML techniques in neuroimaging studies. By doing so, it establishes the theoretical and empirical foundation of this research, positioning it within the broader context of cognitive neuroscience and sex-based brain differences.

2.2 SEXUAL DIMORPHISM IN HUMAN BRAIN

The terms "sex" and "gender" are often used interchangeably in both academic and everyday contexts, leading to considerable confusion and ambiguity. While these terms are related, they represent distinct concepts: sex refers to the biological and physiological characteristics that define males and females, such as chromosomes, hormone levels, and reproductive anatomy, whereas gender pertains to the socially constructed roles, behaviours, and identities that societies attribute to individuals. This distinction is critical in scientific research, as conflating the two can obscure the specific biological mechanisms

under investigation. In this thesis, the term sex is used instead of gender to describe the biological and scientific differences between males and females. By employing this terminology, the study aims to maintain clarity and ensure that the findings are interpreted within the context of biological variability rather than sociocultural influences.

The human brain, in its adult form, is an intricate organ, weighing approximately 1300 to 1400 grams. Its composition is predominantly water (78%), with fat and protein accounting for around 10% and 8%, respectively. On average, male brains tend to exhibit larger volumes compared to female brains (Witelson et al., 2006). These differences are not only limited to brain size but extend to various structural aspects, including the presence of convolutions and folds on the cerebral cortex. These folds are essential for increasing the brain's surface area, thus accommodating more neural cells and facilitating higher cognitive functioning (Garcia et al., 2017).

From birth to death, humans navigate a world marked by inherent sex differentiation that extends beyond physical dissimilarities to encompass distinctions in perception, olfaction, cognition, emotion, and behaviour (Cui et al., 2023; Doty & Cameron, 2009; Escorial et al., 2015; Lukito et al., 2020; Min et al., 2023; Ngun et al., 2011; C. C. Yang et al., 2023). These sex-based differences not only affect individual experiences but also significantly influence life expectancy, susceptibility to sex-specific physical and neurological disorders, and differential responses to medical interventions for both men and women (Borah, 2021; Dai et al., 2015; Mauvais-Jarvis et al., 2021). Another critical facet of this differentiation pertains to the human brain, where sex-based anatomical and functional variations contribute to the phenomenon of sexual dimorphism, which will be explored in this literature review.

Sexual dimorphism broadly refers to variations in size and configuration that distinguish males from females within the same species. This term typically encompasses differences between genetic males and females, particularly secondary characteristics unrelated to reproduction. In humans, such dimorphism manifests across various anatomical traits, including morphological features and brain structures (Nikitovic, 2018). Initial documentation of sexual dimorphism in the human brain appeared in the early

twentieth century, when researchers observed that male brains tend to exhibit greater weight and larger circumferences than female brains (Janowsky, 1989).

This brain dimorphism originates in neurodevelopmental processes, with distinctions evident from early development through childhood, adolescence, and adulthood (Dumitru, 2023). Even after accounting for volume differences, there are observable sex-based developmental trajectories in specific regions, such as the frontal, temporal, and parietal grey matter (Nopoulos et al., 2000; Tanaka et al., 2012). Research has documented differences in cerebral asymmetry across the lifespan, revealing that patterns of asymmetry in neonates differ from those in older children and adults (Dumitru, 2023). These findings suggest that adult cerebral asymmetry patterns emerge prenatally and continue to evolve postnatally under genetic and environmental influences (Gilmore et al., 2007). Asymmetry can be observed as early as 22 weeks' gestation, with males exhibiting a leftward bias (Kivilevitch et al., 2010), while premature infants show a predominantly rightward bias (Dubois et al., 2008). In adults, cerebral asymmetry is characterized by a larger right hemisphere, primarily due to increased right-sided white matter, and fronto-occipital asymmetry, with a larger right prefrontal cortex and a larger left occipital cortex (Nopoulos et al., 2000). White matter volume continues to increase with age, while grey matter peaks around age 10, with females typically reaching this peak earlier in the temporal and frontal lobes (Tanaka et al., 2012).

Differences in structural brain composition and connectivity have substantial implications for cognitive function. Research demonstrates that women generally excel in language-related tasks and verbal fluency, while men show strengths in visuo-spatial abilities and mechanical reasoning (Adani & Cepanec, 2019; Andreano & Cahill, 2009; Collins & Kimura, 1997; Gur et al., 2012; Shaqiri et al., 2018). A study with 28,821 UK Biobank participants examined sex-related differences in cognition and morphometric connectivity using T1-weighted MRI scans. Findings indicated that males have greater global and regional covariance across both hemispheres. Females outperformed in verbal memory, while males excelled in spatial memory. Females also demonstrated faster processing speeds, with no sex differences observed in executive function. The study also

found that greater male structural covariance mediates sex-based differences in verbal memory and processing speed, thus enhancing understanding of the connections between biological sex, cognitive differences, and morphometric connectivity (C. C. Yang et al., 2023).

Sexual dimorphism in the brain underlies a broad spectrum of distinctions between males and females, including susceptibility to psychiatric and neurological disorders as well as age-related neurodegenerative diseases. For example, females show higher prevalence and earlier onset of Alzheimer's disease and general dementia, while males have elevated rates of epilepsy, rapid eye movement (REM) sleep behaviour disorder, and Parkinson's disease (Bergamino et al., 2022; H. Li et al., 2023; X. Li et al., 2023; Liu et al., 2020; Nicastro et al., 2020; Ziukelis et al., 2022). One study examined sex-based neuroanatomical aspects in PD, revealing that male patients experience more pronounced brain atrophy and cortical thickness reduction, primarily in regions such as the cerebellum and frontal, parietal, and temporal lobes. Although both sexes exhibit similar progression patterns, females generally maintain a comparative advantage in these regions over time (H. Li et al., 2023).

Among neurological conditions, females are more prone to migraines, whereas cluster headaches are more common in males. A recent meta-analysis examined grey matter abnormalities in migraine sufferers, revealing reduced grey matter in migraine patients compared to healthy controls, specifically in regions like the posterior insula-opercular areas, prefrontal cortex, and anterior cingulate cortex. A higher percentage of females in the sample correlated with reduced grey matter in the right dorsolateral prefrontal cortex (Dai et al., 2015).

In conclusion, the pervasive influence of sex-based differentiation on human brain structure, cognitive abilities, and susceptibility to neurological conditions establishes a robust foundation for further exploration in this research.

2.3 THE ROLE OF MRI

MRI has revolutionized neuroimaging, providing non-invasive, high-resolution insight into the human brain's structure and function. One critical area where MRI has made substantial contributions is in the study of sexual dimorphism—biological differences in brain anatomy and functionality between males and females. Understanding these differences is not only important for advancing knowledge of brain development but also for identifying how sex-based distinctions might relate to neurological and psychiatric disorders.

Before the invention of MRI, the study of sexual dimorphism in the human brain was largely limited to invasive, post-mortem examination, offering static snapshots of anatomical differences without insight into functional dynamics. For example, Holloway et al. (1993) analysed sexual dimorphism in the human corpus callosum across three independent autopsy samples, focusing on features like total callosal area and splenial width. The study found that, while males generally had larger absolute brain sizes, certain areas of the corpus callosum—especially the splenium—were proportionally larger in females when adjusted for brain size, suggesting structural differences that could relate to cognitive or behavioural variation (Holloway et al., 1993). Such post-mortem findings provided foundational insights into structural sexual dimorphism, although they were inherently limited by their inability to capture the living brain's dynamic processes or account for developmental and environmental influences.

The invention of MRI in the late 20th century transformed the field by enabling non-invasive, high-resolution imaging of living brain structures. MRI works through the principles of magnetic resonance, using powerful magnetic fields and radio waves to produce detailed images of the brain's internal structures without invasive procedures. This revolutionary technology allowed for the *in vivo* examination of brain anatomy and function, enabling researchers to explore sexual dimorphism in the brain more comprehensively. MRI's ability to distinguish between different types of brain tissue and its capacity for longitudinal studies have been especially beneficial for investigating sexual dimorphism, providing insights into brain development, neural connectivity, and hormonal

influences across different life stages. As a result, MRI has expanded our understanding of sex-based differences in brain anatomy, allowing for more accurate observations of how these differences evolve and influence behaviour, cognitive performance, and vulnerability to certain neurological disorders.

In the realm of MRI applications, structural MRI have been instrumental in studying sexual dimorphism. Structural MRI particularly T1-weighted imaging is used to examine structural aspects of the brain. The use of structural MRI to investigate sexual dimorphism in the human brain has been the focus of a vast body of research, offering invaluable insights into how brain structure differs between males and females. A notable recent meta-analysis conducted by Ruigrok et al. (2014) synthesized findings from multiple studies, utilizing a systematic literature search and Gaussian-process regression coordinate-based meta-analysis (GPR-CBMA) to examine sex-based differences in brain volume and tissue density. This meta-analysis analysed data from studies published between 1990 and 2013, focusing on VBM to identify regions exhibiting sexual dimorphism. The main outcomes indicated that males tend to have larger total brain volumes and certain compartmental volumes such as the cerebellum and intracranial volume. Conversely, females often showed relatively higher tissue density in regions such as the insula, hippocampus, and amygdala—areas linked to emotion, memory, and social cognition (Ruigrok et al., 2014).

Despite the breadth of research in this area, variability in methodological approaches has emerged as a significant limitation, particularly in the application of volumetric analyses. Studies often diverge in their use of techniques such as VBM versus VOI analyses. VBM enables for whole-brain, voxel-wise analyses, offering unbiased detection of sex-related differences, while VOI studies focus on preselected brain regions, which might limit the scope of findings but provide more targeted insights. This methodological inconsistency raises questions about the generalizability and consistency of findings, motivating further investigation to unify and expand on these approaches (Ruigrok et al., 2014). Furthermore, the reliance on traditional univariate statistical methods has sparked debate, as studies report varying results regarding the extent and significance of sex-related differences in grey matter properties (Ingalhalikar et al., 2014; Wierenga et

al., 2022). For instance, while male brains are consistently reported to be 8–15% larger than female brains, a distinction that emerges during early development and persists throughout life (Dumitru, 2023; Witelson et al., 2006). Despite these observations, some researchers argue that the substantial overlap exists between sexes and that localized differences are of limited biological consequence (Joel, 2021; Joel et al., 2018). These contrasting perspectives highlight the complexity of interpreting sex-related neuroanatomical variation and emphasize the need for more nuanced, integrative approaches to reconcile these discrepancies.

A novel dimension of this research involves examining the unique interplay between sexual dimorphism and the effects of intensive cognitive training, specifically among Huffaz (individuals who memorize and recite the Quran). This focus represents a significant contribution to the field, as little research has explored how sex-based brain differences may mediate the impacts of rigorous cognitive practices. This investigation will not only address gaps in methodology but also shed light on the broader implications of sexual dimorphism in learning, memory, and cognitive adaptation.

2.4 HUFFAZ AND COGNITIVE NEUROPLASTICITY CHANGES

The term "Huffaz" (singular: Hafiz) refers to Muslims who have memorized the entire Quran, a holy text comprising 114 chapters (Surahs) and 6,236 verses (Ayahs), totalling over 77,000 words. This practice has been integral to Islamic culture since the era of the Prophet Muhammad (PBUH), serving both as a spiritual exercise and a means of preserving the Quranic text across generations. During the golden age of the Islamic world, memorizing the Quran was often seen as a foundational step for scholars before they pursued studies in various scientific fields, such as medicine, mathematics, and astronomy (Keblawi, 2014). Memorization remains a respected and cherished achievement within

Islamic communities, often motivated by religious rewards, spiritual benefits, and the desire to maintain a deep, personal connection to the Quran.

The process of becoming a Hafiz is typically rigorous and structured, often beginning in childhood and taking several years of consistent effort. Huffaz dedicate hours each day to memorize and recite portions of the Quran under the guidance of an instructor. For many, this journey spans three to four years, though the timeline varies depending on the individual's memory capacity, linguistic background, and dedication. For non-native Arabic speakers, the process can be especially challenging due to the need to learn not only the verses but also the unique pronunciation and grammatical rules of classical Arabic, which differ significantly from modern Arabic and are often unfamiliar to learners.

Memorizing the Quran requires a methodical approach involving repetitive learning, which is crucial for encoding verses into long-term memory. Each memorized section is typically reviewed and recited in the presence of a teacher to ensure accuracy, as the preservation of the text demands strict adherence to pronunciation and recitation rules. The process also involves simultaneous revision of previously memorized verses while adding new ones, an ongoing cycle of retention and acquisition that reinforces memory through frequent repetition (Kebrawi, 2014). This review process, known as "Muraja'ah," is essential to prevent forgetting and to ensure that the memorized text remains intact over time. As Huffaz progress, they continuously repeat both new and old portions, creating a dynamic interplay between different memory systems and cognitive faculties.

The cognitive demands of Quranic memorization are immense, and studies suggest that such rigorous mental exercises may stimulate neuroplasticity—the brain's ability to reorganize itself by forming new neural connections (Jamaludin et al., 2022). Neuroplasticity is particularly relevant in activities that require both memory encoding and retrieval, language processing, and cognitive control. The repetition involved in Quranic memorization engages the brain's memory centres, including the hippocampus and regions associated with language and auditory processing. Moreover, for Huffaz who are non-native Arabic speakers, the process activates brain areas responsible for second language

acquisition, potentially enhancing cortical thickness in regions tied to linguistic and phonetic comprehension.

Memorizing the Quran is also unique compared to other forms of memorization, as it involves not only rote memory but also a deep level of linguistic and phonetic precision. Unlike conventional learning, which may allow flexibility in recall, the memorization of the Quran mandates exact recall down to the pronunciation of each word. This precision requires Huffaz to engage multiple sensory modalities: visual processing as they read the script, auditory processing as they recite and listen, and motor memory as they practice recitation. This multisensory involvement is believed to stimulate neuroplastic changes across various regions of the brain, including the frontal lobe, which is associated with executive function, attention, and memory consolidation.

The memorization process also has implications beyond linguistic and memory skills. There is a growing interest in understanding how the brain of a Hafiz adapts to the intensive memorization task, especially considering recent studies that show structural brain changes in individuals engaged in demanding cognitive tasks. For example, studies on London taxi drivers revealed that extensive spatial navigation training increased the size of their posterior hippocampus, a region linked to spatial memory (Maguire et al., 2000). Similarly, musicians have shown increased grey matter volume in motor, auditory, and visuospatial brain regions due to long-term training and repetition (Gaser & Schlaug, 2003). These findings provide a foundation for hypothesizing that the extensive cognitive activity involved in Quran memorization could lead to neuroplastic adaptations in Huffaz, specifically in brain regions associated with memory, language, and learning.

A groundbreaking study using MRI have begun to explore these neuroplastic changes in the brains of Huffaz (Jamaludin et al., 2022). They used VOI-based analysis to examine brain structures in Huffaz compared to non-Huffaz. The results indicated structural differences in several brain areas, suggesting that the Quranic memorization process could contribute to localized brain adaptations. The VOI-based analysis revealed that specific brain areas, such as the angular gyrus and medial temporal gyrus, were structurally distinct in Huffaz, likely reflecting the impact of intense memorization on these regions.

Building on these findings, the current Ph.D. research aims to investigate sexual dimorphism and to further explore the effect of neuroplastic changes associated with Quranic memorization among Huffaz. This study seeks to address methodological gaps, such as the variability in measurement approaches (e.g., VBM vs. VOI analysis), which have previously limited generalizability in studies of brain plasticity. Moreover, a key novelty of this Ph.D. research is examining the impact of intensive cognitive training, specifically in Huffaz, on sex-based brain differences, providing a new perspective on the interplay between cultural practices and neuroplastic adaptation.

These insights pave the way for further research into the neuroplastic effects of Quranic memorization, including investigations into how these structural changes relate to cognitive functions. Understanding the neurological adaptations of Huffaz not only broadens our knowledge of neuroplasticity in religious and cultural practices but also raises intriguing questions about the potential cognitive benefits associated with extensive textual memorization. This research has broader implications for cognitive neuroscience, offering insights into how cultural practices may uniquely shape brain structure and function over time.

2.5 VOLUMETRY AND COMPLEXITY MEASUREMENT OF MRI BRAIN IMAGE

The study of brain structure can be approached from various angles, each capturing distinct aspects of neuroanatomy. In this work, the author incorporated both volumetric and complexity measurements to gain a more comprehensive understanding of sexual dimorphism in brain structure. The key distinction between these two methods lies in the type of information they provide about brain morphology.

2.5.1 Volumetry

2.5.1.1 *Principle of volumetry in brain MR Imaging*

Volumetric measurement is a cornerstone of modern neuroimaging research, offering a quantitative approach to understanding the structural properties of the brain. The fundamental principle of volumetry lies in accurately segmenting brain structures from MRI data and computing their volumes based on voxel-level information. MRI scans are composed of voxels, which are the smallest measurable units in a three-dimensional (3D) image, like pixels in two-dimensional (2D) images but with depth. Each voxel has a predefined volume (e.g., 1 mm³), and volumetry calculates the total number of voxels within a specific brain region to derive its overall volume. By estimating the 3D volume of specific regions of interest, volumetry provides critical insights into normal and pathological brain processes. The importance of volumetric analysis lies in its ability to identify and quantify subtle changes in brain structures, which are often associated with neurodegeneration, developmental processes, and psychiatric conditions (Ashburner & Friston, 2000).

Brain volume measurement is relatively straightforward to interpret and benefits from a well-established base of normative data across various populations and age groups. In a clinical setting, this makes it a highly valuable diagnostic tool, allowing clinicians to compare an individual's brain structure against standardized benchmarks. This comparison enables the detection of abnormalities, such as the size and progression of tumours, by providing precise volumetric measurements. These metrics help clinicians track tumour growth or shrinkage, monitor treatment effectiveness, and make informed decisions regarding intervention strategies. The ease of use and reliability of brain volume measurement make it essential for accurate and timely pathology assessment in clinical practice.

The widespread availability of advanced software and MRI protocols enhances the utility of brain volume measurement in research and clinical. Key tools include Statistical Parametric Mapping (SPM) from University College London (UCL), which excels at statistical analysis of brain imaging, particularly for functional MRI, positron emission tomography (PET), and structural MRI, making it useful for detecting abnormalities like tumours. FreeSurfer, developed by the Laboratory for Computational Neuroimaging at Massachusetts General Hospital, is known for its automated segmentation of cortical and subcortical structures, ideal for tracking changes in brain volume over time. The FMRIB Software Library (FSL) from Oxford's Centre for Functional MRI of the Brain (FMRIB) provides comprehensive tools for processing structural, diffusion, and functional MRI, making it highly effective for brain volume measurement and abnormality detection. These tools streamline diagnosis and monitoring in especially research settings.

2.5.1.2 The role of volume analysis in exploring healthy human brain morphology and its significance in brain disorders

MRI has emerged as the preferred modality for brain research due to its non-invasive nature and superior imaging capabilities. Laboratory-based techniques, such as histological analysis, provide valuable information about brain structure at the microscopic level but are invasive, requiring tissue samples, and are therefore impractical for longitudinal studies or large-scale research. MRI, by contrast, offers detailed, 3D *in-vivo* representations of the brain, enabling repeated assessments to track changes over time. Furthermore, MRI's ability to differentiate between grey matter, white matter, and cerebrospinal fluid allows for comprehensive analysis of brain morphology. These advantages make MRI a powerful tool for studying both healthy and pathological brains. Additionally, MRI's high resolution and accuracy allow for the early detection of subtle structural changes that may not be

observable through other methods (Zhao et al., 2023). This non-invasive approach also supports the study of neurodevelopment and disease progression, making it invaluable in both research and clinical settings (Gaurav et al., 2021; Y. Wang et al., 2024).

Brain volumetry provides critical insights into the structural dynamics of the brain, yielding information that spans multiple domains. Volumetric changes are often the earliest detectable markers of neurodegeneration. Grey matter volume reductions indicate neuronal loss and synaptic dysfunction, commonly observed in Alzheimer's disease and Parkinson's disease (H. Li et al., 2023; Rodrigo et al., 2023; Seyedsalehi et al., 2023). Brain volumetry also provides a window into the dynamic processes of neurodevelopment and plasticity. During childhood and adolescence, volumetric increases in certain brain regions are indicative of synaptic proliferation, while subsequent reductions reflect synaptic pruning essential for efficient neural functioning (Dumitru, 2023; Y. Wang et al., 2024; Zhao et al., 2023). Such measurements also capture brain remodelling associated with learning, memory formation, and recovery from injury. Structural volumetric data also reveal the relationship between brain anatomy and cognitive or emotional functions. For instance, larger hippocampal volumes correlate with better memory performance, while smaller amygdala volumes are often linked to emotional dysregulation in psychiatric disorders (Maguire et al., 2000; Mohammadi et al., 2023; Suppa et al., 2015).

2.5.1.3 Method of image processing and analysis

In the domain of volumetric analysis, two primary methodologies dominate: VBM and VOI analysis. Each method offers distinct advantages and serves complementary purposes in volumetric research. VBM is an automated, voxel-wise technique that identifies regional differences in grey matter and white matter volumes across the entire brain without predefined hypotheses. This method is particularly useful for detecting widespread and subtle structural changes, making it ideal for exploratory studies involving large datasets

(Ashburner & Friston, 2000). In contrast, VOI analysis is a hypothesis-driven approach that involves the segmentation and volumetric quantification of specific brain regions based on anatomical landmarks (Wierenga et al., 2022). This method provides high precision and reliability for studying targeted areas, such as the hippocampus, amygdala, or thalamus, which are frequently implicated in neurodegenerative and psychiatric disorders (Matte Bon et al., 2024). While VBM excels in hypothesis-free exploratory analyses, VOI offers greater precision for targeted investigations. Integrating these two approaches provides a robust framework for examining both global and regional volumetric changes. This dual methodology allows for a comprehensive assessment of the structural alterations associated with neurological and psychiatric conditions.

This doctoral research leverages both VBM and VOI methodologies to investigate volumetric changes in brain MRI data. By combining the strengths of these techniques, this study aims to identify global structural changes using VBM while validating specific regional findings through VOI analysis. This integrative approach ensures a nuanced understanding of the condition under investigation and enhances the reliability and generalizability of the findings. Ultimately, by uniting these methodologies, this research seeks to advance the understanding of brain volumetric changes in health and disease, contributing to the broader field of neuroimaging and neuroscience. However, one limitation of volume measurement is that it provides only a macroscopic view of brain structure. While it is effective in detecting gross atrophy or enlargement, it does not capture the fine-grained details of the brain's structural complexity, such as the intricacies of cortical folding or surface irregularities.

2.5.2 Complexity measure

2.5.2.1 *Principle of complexity in brain MR Imaging*

Complexity measurements, on the other hand, provide information on the intricacy of brain surface geometry, examining how convoluted or irregular brain structures are. FD analysis is a widely utilized technique for evaluating brain complexity, as it quantifies surface complexity across multiple scales, leveraging the fractal properties inherent in the human cerebral cortex (Free et al., 1996). Unlike volumetric analysis, which focuses on size, FD analysis captures the intricate folding patterns and structural irregularities that contribute to the brain's functional capabilities. Complexity measurements offer a more detailed understanding of how brain regions are organized and may reveal sex-related differences in brain structure that are not evident through volume measurements alone. These subtle differences in cortical and subcortical organization are crucial for understanding how the brain supports cognitive and behavioural functions, which may vary between males and females.

The concept of fractals was introduced by the French mathematician Mandelbrot in the 1970s. In his paper titled "How long is the coast of Britain? Statistical self-similarity and fractional dimension," Mandelbrot emphasized that many natural objects are incredibly complex and irregular, making them difficult to describe using simple geometric primitives (B. Mandelbrot, 1967). He highlighted the presence of strong self-similarity in such complex objects. The coastline of Britain was used as a prime example of a fractal, demonstrating accurate or statistical self-similarity (B. B. Mandelbrot, 1982, 1985).

Mandelbrot's key insight was that self-similarity is the central feature of fractals. This means that fractal objects can be divided into numerous parts, with each part resembling a smaller-scale copy of the whole object or exhibiting statistical similarities. However, the formalization of the term "fractal" and the development of algorithms for measuring the FD of images occurred later, in 1983, through Mandelbrot's work, "The Fractal Geometry of Nature" (B. B. Mandelbrot, 1982). This work introduced fractals as

geometric objects characterized by self-similarity, displaying a repetitive structure across various scales. As a result, many scholars have adopted FD, or sometimes referred to as the Hausdorff dimension, as a key indicator for describing the level of self-similarity and complexity in geometric structures.

The Sierpiński triangle (Figure 2.1) is a classic example of a self-similar fractal, constructed by recursively subdividing an equilateral triangle and removing the central portion at each iteration (Image adopted from (Guariglia, 2018)). The resulting structure exhibits self-similarity, where each part resembles the whole at increasingly smaller scales. As the number of iterations grows, the Sierpiński triangle approaches a shape with infinite complexity yet occupies zero area in the limit. This iterative process also highlights the fractal's non-integer FD of approximately 1.585, which indicates its intermediate nature between one and two dimensions. The visual representation effectively demonstrates how removing the central portions at each step generates a pattern of ever-smaller triangles, leading to the distinctive appearance of the Sierpiński triangle.



Figure 2.1 Iterative construction of the Sierpiński triangle.

Fractal analysis has been successfully applied to a wide range of natural phenomena, including the measurement of the British coastline (where its application originated), the study of mountains, clouds, and various biological structures. Thanks to its proficiency in quantifying complex and intricate structures, fractal analysis has emerged as a universal tool for the analysis and quantification of geometric complexity in natural objects, including the human brain.

2.5.2.2 The role of fractal analysis in exploring healthy human brain morphology and its significance in brain disorders

Brain morphometry, which involves the quantitative assessment of brain structure, plays a vital role in comprehending brain development, aging, and the pathology of neuropsychiatric and neurodegenerative diseases. Previous literature highlights several key applications of fractal analysis in brain morphometry research. A comprehensive systematic review was undertaken by a team of researchers from Italy, encompassing clinical and nonclinical populations (Meregalli et al., 2022). The authors delineated four primary applications of fractal analysis: FD assessment in healthy individuals, its utilization in psychiatric disorders, its role in neurological disorders, and its applicability in various other medical conditions. This review focused on its application towards healthy individuals as well as psychiatric and neurological disorder.

A series of recent studies have demonstrated the invaluable application of fractal analysis in assessing brain complexity and exploring lifespan and sex differences in healthy human brain. Chen et al. (2023) examined the impact of normal aging and sex on subregional cortex alterations using FD analysis, revealing significant differences across developmental stages across Chinese population. Cui et al. (2023) investigated age and sex-related disparities in cortical brain morphology among middle-aged and older adults shedding light on notable sex differences and their implications for cognitive performance. Furthermore, Del Mauro et al. (2022) employed various techniques to investigate sexual dimorphism in human brain structure, with FD revealing differences in cortical complexity across sexes. Sandu et al. (2014) studied post-adolescent (age group 13-14 vs age group 20-30) developmental changes in cortical complexity, uncovering both common and sex-specific alterations, with FD as a key metric. Finally, Farahibozorg et al. (2015) delved into age- and sex-related variations in the brain's white matter FD, emphasizing its potential to describe structural and functional changes throughout adulthood. These studies collectively

underscore the versatility and significance of fractal analysis in enhancing our understanding of the healthy human brain's intricate structural properties, from developmental processes to cognitive function and individual variations.

Fractal analysis has also emerged as a powerful tool in the realm of neuropsychiatric and neurodegenerative disease research, shedding light on structural intricacies and their implications. In Porcaro et al.'s study (2022) FD analysis revealed structural changes in the hypothalamus during migraine attacks, offering insights into the modulation of attack duration. Tu et al. (2022) utilized surface-based morphometry to investigate cortical morphology in fibromyalgia patients, unveiling neuroanatomical aberrations and their potential neuropathological relevance. Moreover, Paun et al. (2022) applied fractal analysis to detect neural disabilities in the context of multiple sclerosis, showcasing its potential as a diagnostic tool. Additionally, Roura et al. (2021) analysed longitudinal changes in brain fractal geometry to predict disability progression in multiple sclerosis patients, underscoring its role in prognostic assessments.

In the realm of dementia research, Nicastro et al. (2020) explored the patterns of cortical thickness and FD changes in Alzheimer's disease (AD) and frontotemporal dementia (FTD). They revealed distinct cortical complexity correlates of cognitive domain impairment, potentially serving as a diagnostic marker. Nenadic et al. (2017) explored bipolar disorder, identifying early neurodevelopmental pathologies through FD analysis. Lastly, (Ruiz de Miras et al. (2017) highlighted the utility of fractal analysis in differentiating between healthy brains and those affected by schizophrenia or bipolar disorder, utilizing FD as a disease marker.

Collectively, these studies illustrate the diverse applications of fractal analysis in understanding the structural complexities and alterations within the normal brain and various brain diseases, offering valuable insights for both diagnosis and prognosis.

2.5.2.3 Fractal image analysis methods

Researchers employ various methods of fractal analysis to measure the complexity of these structures. In this thesis, two distinct methods were used to evaluate the complexity of brain morphology, providing complementary insights into its structural characteristics:

a) Box counting method

Box-Counting Fractal Dimension (BC FD) is one of the simplest and commonly used method employed to determine the FD of an object. It involves overlaying a grid of boxes with varying sizes over a two-dimensional or three-dimensional image of the brain. The number of boxes required to cover the brain structure is counted at each scale, and the FD is computed by analysing how the number of boxes scales with the size of the boxes.

The procedure for calculating BC FD consists of two primary steps. First, a mesh composed of minimum box sizes (r) is used to cover the entire image. The second step involves enumerating the number of boxes (N) required to cover the object of interest. The FD value can then be derived by assessing the gradient between the logarithm of the number of boxes (N) and the logarithm of the box size (ϵ). The equation for the box-counting fractal dimension is as follows:

$$FD = \frac{\log \text{Number of boxes (N)}}{\log \text{Box sizes (1/\epsilon)}} \quad (1)$$

where box size (r) will decrease proportionally and the number of boxes (N) filling the image will increase accordingly to calculate the FD of the image. An example of box-

counting method as explained by Wu et al. (2020) is shown in Figure 2.2 and Figure 2.3. In Figure 2.2, altering the side length of the boxes (from a-f) results in a change in the number of boxes required to cover the figure (Adopted from Wu et al., 2020). When the side length is reduced significantly approaching zero, the boxes tend to precisely cover the actual fractal. Then Figure 2.3 described the plotting $\log N$ vs $\log \epsilon$ gives a straight line, the coordinate system used systematically which varying the side length value ϵ of the box to find its corresponding N (Adopted from Wu et al., 2020).

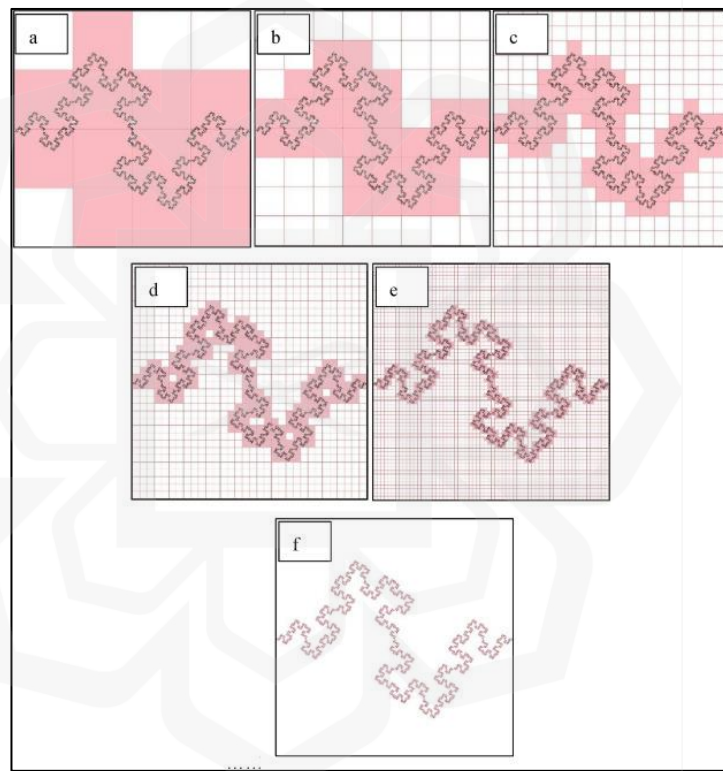


Figure 2.2 An example of box-counting fractal dimension.

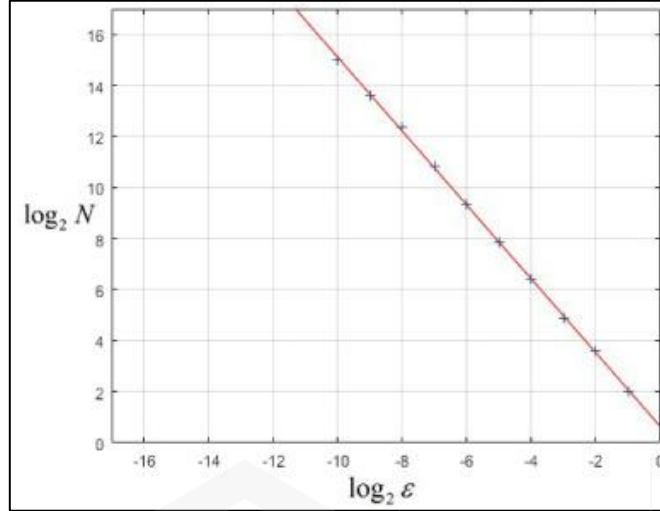


Figure 2.3 Plotting of box-counting fractal dimension.

However, BC FD albeit widely accepted, reliable and simple to compute it also possesses certain limitations (Meregalli et al., 2022). It heavily relies on user input for the placement of the box grid on images, employs a global thresholding approach, and necessitates binary segmentation (in black and white) before applying the BC FD algorithm for FD calculation. These factors can introduce errors, whether due to operator-dependent actions or distortions from automatic algorithms. Consequently, misregistration of structures, particularly at the grey-white matter border, may occur, leading to inaccurate FD values. To address these challenges, a more advanced and effective FD calculation, known as Fourier fractal dimension (FFD), has been developed.

b) Fourier fractal method

The Fourier Fractal Dimension (FFD) represents a greyscale-level approach to fractal analysis, designed for quantifying 3D images (Russ, 1994). In contrast to the box-counting FD, the FFD algorithm shifts its zero frequency to the centre of the images. The Fourier method samples the images in a circular pattern radiating from the centre, traversing from zero frequency to higher frequencies. This methodology has previously been employed by the supervisor of this doctoral study, Prof Dr Zulfaezal Che Azemin on retinal vasculature (Azemin et al., 2011) and he has also been implemented in brain imaging analysis for population of Quranic memorizers (Jamaludin et al., 2022). Based on his recent work (Che Azemin et al., 2024), the Figure 2.4 depict retinal vascular images utilized to evaluate the FD of the eye's vascular network across different age groups. The first image (left) illustrates a higher FD of 1.75, typically found in younger individuals, indicating a more intricate and evenly distributed vascular structure. Conversely, the second image (right) displays a lower FD of 1.69, characteristic of older individuals, demonstrating a decline in the complexity and density of the vascular network.

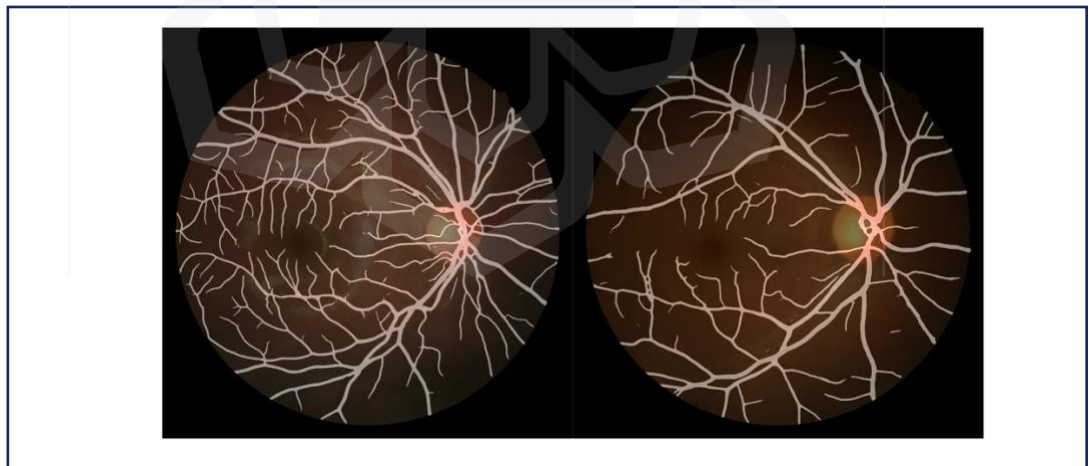


Figure 2.4 Retinal vascular images showing differences in fractal dimension (FD) between younger and older individuals.

FFD presents numerous advantages over box-counting FD in fractal analysis. FFD eliminates the requirement for converting images into binary format, negates the need for image segmentation, and offers operator independence. This makes it conducive for automated image analysis, with potential applications in clinical settings (Azemin et al., 2011; Russ, 1994).

In conclusion, the study of brain structure can be approached from various angles, each capturing distinct aspects of neuroanatomy. By combining both volumetric and complexity measurements, this research aimed to provide a more holistic view of brain sexual dimorphism. While volumetric analysis identified larger brain regions in males and females, complexity analysis using FD offered a deeper understanding of the structural intricacies that may underlie functional differences. Together, these approaches allowed us to explore not only the overall size of brain regions but also the intricate patterns of brain folding and organization, contributing to a more nuanced understanding of how sex differences manifest at both macro and micro-structural levels.

2.6 ARTIFICIAL INTELLIGENCE ADVANCEMENTS IN NEUROIMAGING

AI is a prominent subfield of computer science that is dedicated to the development of systems and machines capable of executing tasks traditionally requiring human intelligence. These tasks encompass a wide spectrum of cognitive functions, including reasoning, learning, problem-solving, understanding natural language, pattern recognition, and decision-making. AI systems are designed to emulate or replicate human cognitive processes, which enables them to perform complex activities either autonomously or with minimal human intervention. The rapid evolution of AI has been significantly fuelled by advancements in ML and Deep Learning (DL), which represent two foundational and

transformative subfields within AI. These techniques have revolutionized numerous disciplines, including image recognition, natural language processing, medical diagnosis, and more.

In the realm of neuroimaging, the integration of ML techniques with brain MRI has heralded a new paradigm in medical diagnostics and research. This synergy between AI and neuroimaging has fundamentally transformed how neurological disorders are understood, diagnosed, and predicted, presenting novel opportunities for early disease detection, precision diagnostics, and personalized treatment planning. Using advanced ML and DL algorithms, AI has enabled unprecedented insights into the complex structures and functioning of the brain, facilitating the identification of subtle biomarkers and patterns that would be otherwise undetectable by traditional diagnostic methods.

This subchapter aims to delve into the fundamental principles of both ML and deep learning, providing an overview of their underlying mechanisms and how they have been applied in neuroimaging. Furthermore, it will introduce the models used in this study, specifically those employed for the analysis of brain MRI data. The models utilized in this research include Logistic Regression (LR), Support Vector Machines (SVM), and Random Forests (RF) for machine learning, as well as Multi-Layer Feed-Forward Artificial Neural Networks (ANN) for deep learning. The selection of these models was informed by both a systematic review of existing literature and the specific capabilities offered by the AI studio software, which will be explored in greater detail in subsequent sections of this chapter. By examining the performance and applicability of these models in neuroimaging, this study seeks to contribute to the growing body of knowledge on AI's role in advancing diagnostic and therapeutic practices in neurology.

2.6.1 Principle of machine learning

ML is a subfield of AI that is concerned with the development and application of algorithms and statistical models that enable computers to learn from data, make predictions, and make decisions without being explicitly programmed. At its core, ML focuses on enabling systems to improve their performance over time by identifying patterns within data and utilizing these patterns to inform future predictions or decisions. ML algorithms can be broadly categorized into three primary types: supervised learning, unsupervised learning, and reinforcement learning. In supervised learning, a model is trained using labelled data, where both the input features and corresponding output labels are provided. The model learns to map the input features to the correct output based on this training data. In contrast, unsupervised learning involves working with unlabelled data and aims to uncover hidden structures or patterns within the data, such as clustering similar data points or reducing the dimensionality of complex datasets. Reinforcement learning, another key category of machine learning, is based on an agent interacting with an environment and learning through trial and error. The agent receives feedback in the form of rewards or penalties, and over time, it refines its actions to maximize cumulative rewards, making it particularly useful for decision-making in dynamic environments.

Within the realm of machine learning, there is a vast array of methods or models that can be applied to different types of problems. For this study, we focus on three widely recognized and relatively simple yet powerful ML algorithms: Logistic Regression (LR), Support Vector Machines (SVM), and Random Forest (RF). These models were selected for their effectiveness in classification tasks, their interpretability, and their ability to handle various types of data.

LR is a widely used supervised learning algorithm, particularly for binary classification tasks. The goal of LR is to model the probability of a binary outcome based on one or more input features. The logistic function (also known as the sigmoid function) is employed to constrain the predicted probability between 0 and 1, allowing the model to output a probability score for each instance. Despite its simplicity, LR remains highly

popular due to its interpretability and efficiency. It is particularly favoured in fields like healthcare, finance, and social sciences, where understanding the relationship between input features and the predicted outcome is crucial. In healthcare, for example, LR can be used to predict the likelihood of disease occurrence based on clinical features.

SVM are another powerful supervised learning technique, primarily used for classification tasks but also applicable to regression problems. SVM aims to find the optimal hyperplane that separates different classes in the feature space, maximizing the margin between the closest data points of each class, known as support vectors. One of the major strengths of SVM is its ability to effectively handle high-dimensional data, which makes it suitable for complex tasks such as text classification, image recognition, and bioinformatics. Furthermore, SVM's flexibility is enhanced by the kernel trick, which allows it to efficiently map data into higher-dimensional spaces to solve non-linear classification problems. This makes SVM particularly valuable in situations where the decision boundaries between classes are not linearly separable in the original feature space.

RF, an ensemble learning method, leverages the power of decision trees to perform both classification and regression tasks. The RF algorithm constructs a collection of decision trees during the training process, where each tree is trained on a random subset of the data and input features. When making predictions, the model aggregates the output from all individual decision trees, typically by taking the majority vote for classification tasks or averaging the predictions for regression tasks. This ensemble approach enhances the model's robustness, as it mitigates the risk of overfitting, which is a common issue in individual decision trees. RF is particularly advantageous in handling large datasets with numerous features, as well as datasets with mixed data types (continuous and categorical). It has been widely applied in various fields such as bioinformatics, finance, and environmental science, and is known for its high predictive accuracy, interpretability, and ability to deal with noisy or missing data.

In conclusion, ML provides a diverse toolkit of algorithms that can be tailored to a variety of applications across different fields. The algorithms discussed—LR, SVM, and RF—represent a selection of foundational models that form the basis of many successful

ML applications. Their robustness, interpretability, and scalability make them particularly well-suited to addressing complex problems, including those encountered in medical and neuroimaging research, which is the primary focus of this study. Each of these models has its strengths and limitations, and their selection for this research study was informed by both theoretical considerations and empirical evidence from the literature.

2.6.2 Principle of deep learning

Deep learning is a specialized subset of ML that utilizes artificial neural networks with multiple layers—commonly referred to as deep neural networks (DNNs)—to model and learn from large and complex datasets. These models have revolutionized the field of AI by their ability to automatically extract hierarchical features from raw data, enabling them to process intricate inputs such as images, speech, and text. Unlike traditional ML algorithms that rely on manually engineered features, deep learning models can autonomously discover intricate patterns and representations, making them highly effective for tasks that require high levels of abstraction. This capability has led to breakthroughs in a wide range of applications, including natural language processing, computer vision, speech recognition, and even areas such as autonomous driving.

Within deep learning, various methods and architectures exist, each suited to specific types of data or tasks. For the current research, however, the focus is on a particular deep learning method implemented in the AI software used in this study: the Multi-Layer Feed-Forward ANN. A multi-layer feed-forward ANN is a type of deep neural network comprising multiple layers of interconnected neurons. The structure of this network includes three main components: the input layer, hidden layers, and the output layer. The input layer receives the raw data, which is then passed through one or more hidden layers, where the network learns to transform the data into higher-level representations. Finally, the output layer produces the network's predictions or classifications.

The network learns by iteratively adjusting the weights of the connections between neurons during training. This process is typically achieved through a technique known as backpropagation, wherein the model calculates the error between its predicted outputs and the true labels. The error is propagated backward through the network, and the weights are updated to minimize this discrepancy, usually using optimization algorithms such as stochastic gradient descent. As a result, the network progressively improves its ability to make accurate predictions or classifications.

Multi-layer feed-forward ANNs are highly versatile and can be applied to a broad spectrum of tasks, including classification, regression, and even more advanced applications like image generation or sequence modelling. Their flexibility, combined with the capacity to handle vast amounts of data and complex patterns, makes them particularly effective in domains such as image recognition, natural language processing, and medical diagnostics, where data complexity and volume can be substantial. In the context of this study, the use of such a deep learning model is motivated by its ability to learn complex patterns from neuroimaging data, particularly in brain MRI, and offer insights into neurological conditions with remarkable accuracy.

2.6.3 Comparison between machine learning and deep learning

Both ML and DL share the common goal of extracting meaningful patterns and insights from data. However, they differ significantly in terms of their approach, complexity, and computational demands. These differences manifest in several key areas: data requirements, interpretability, and computational complexity.

One of the most fundamental distinctions between ML and DL lies in their data requirements. Deep learning models typically necessitate vast amounts of labelled data to achieve optimal performance. This is because deep learning algorithms, particularly those involving deep neural networks, require large datasets to effectively train the numerous

layers and parameters within the network. The sheer volume of data allows these models to capture intricate patterns and representations. In contrast, traditional ML models, such as LR, SVM, and RF, can perform effectively even with relatively smaller datasets. These models rely on a more direct relationship between features and outcomes, enabling them to function well even when the available data is limited.

Another key difference is in interpretability. ML models such as LR and RF are generally more interpretable compared to deep learning models. For instance, logistic regression provides clear insights into the influence of each feature on the outcome through its model coefficients, which directly indicate feature importance. Random forests, while more complex, offer interpretability through the aggregation of individual decision trees, each of which can be examined for the rules it applies to classify data. On the other hand, deep learning models, particularly deep neural networks, are often considered "black box" models due to their intricate structure and large number of parameters. This lack of transparency makes it challenging to understand how these models arrive at a particular prediction, which can be a limitation in fields that demand high levels of explainability, such as healthcare and finance.

In terms of computational complexity, deep learning models are significantly more demanding. The process of training deep neural networks involves adjusting millions, or even billions, of parameters through complex algorithms such as backpropagation. This requires substantial computational power, particularly when dealing with large datasets that contain a large number of features. For such tasks, specialized hardware, such as Graphics Processing Units (GPUs), is often employed to accelerate model training. In contrast, traditional ML models like LR, SVM, RF is less computationally intensive. These models can be trained and executed on standard hardware, making them more accessible for applications where computational resources are limited or where quick model training and deployment are necessary.

In this thesis, the choice of ML and DL models was influenced by the small sample size of the data collected. Given the limited availability of data, the study focused on ML models, which are well-suited for smaller datasets and do not require the large volumes of

labelled data that deep learning models typically demand. Consequently, traditional ML algorithms, such as LR, SVM, and RF, were prioritized, as they can efficiently handle smaller datasets and provide more interpretable results.

However, despite the limited data, one deep learning model was employed for comparison. Specifically, a multi-layer feed-forward ANN was selected from the available AI software, as it offers the potential to capture more complex patterns in the data. This deep learning model, although computationally intensive and typically requiring larger datasets, was included in the analysis due to its demonstrated success in various applications and its ability to learn hierarchical representations of data. In this thesis, the use of a single deep learning model was a strategic decision, balancing the need for sophisticated pattern recognition with the constraints imposed by the small sample size.

2.6.4 Application of machine learning and deep learning in neuroimaging

ML and DL have been used in many applications in neuroimaging. Since deep learning is a subset of machine learning, for the sake of simplicity, this subtopic will use the term "machine learning" to refer to both ML and DL models collectively. One significant area of application is the development of diagnostic biomarkers for neurological disorders. For instance, ML techniques are being used to analyse MRI data to identify markers for diseases like obsessive-compulsive disorder (OCD), brain tumours, attention deficit hyperactivity disorder (ADHD), and schizophrenia. These techniques allow for accurate disease classification and can offer insights into neural correlates that were previously challenging to identify. In one study, SVM were employed to achieve an impressive 94% cross-validation accuracy in classifying patients with OCD, demonstrating the complementary role of various MRI indices within and outside relevant brain circuits (Huang et al., 2023). For brain tumour classification, a study explored the use of FD measures in distinguishing between low-grade and high-grade gliomas, achieving high accuracy, sensitivity, and

specificity (Battalapalli et al., 2023; Wahlang et al., 2022). Additionally, ML approaches helped differentiate ADHD and typically developing children based on structural brain MRI and personal characteristics, obtaining a high classification accuracy (Lohani & Rana, 2023). These findings underline the potential of ML in MRI-based diagnostics and emphasize the critical role of various features in enhancing accuracy and understanding complex brain disorders.

Moreover, MRI and ML provides a promising substitution of costly, not readily accessible and ionising radiation-exposing PET scans. MRI, a widely available and non-invasive imaging modality, is being harnessed in a study along with deep learning techniques to predict amyloid-tau-neurodegeneration (ATN) biomarker status. This not only addressing both financial and safety concerns associated with PET scans but also opens the potential for non-invasive characterization of ATN status, a significant advancement in Alzheimer's disease research (Lew et al., 2023).

ML has also made inroads in early disease detection, particularly in neurodevelopmental disorders and schizophrenia. In a longitudinal cohort study, ML techniques are being employed to analyse neuropsychological functions and brain development, ultimately predicting the onset of neurodevelopmental disorders in preterm infants such as autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD). This approach holds promise in identifying early biological predictors and environmental risk factors for later neurodevelopmental disorder outcomes (Zhao et al., 2023). In the realm of schizophrenia, ML and neuroimaging data are harnessed to distinguish between patients and healthy controls, offering early diagnosis and potential neuroimaging risk factor insights (Steardo et al., 2020). Additionally, deep convolutional neural network (CNN) architectures are being explored for early Alzheimer's disease detection from brain MRIs, offering a remarkable three-class accuracy of 99.05% (Rodrigo et al., 2023). These developments underscore the potential of ML in combination with MRI for early diagnosis, characterization, and intervention in a range of neurodevelopmental and psychiatric disorders, ultimately providing opportunities for timely and effective patient care.

Machine learning's reach extends beyond diagnostics to the prediction of disease progression, aiding in effective treatment planning. In the case of multiple sclerosis (MS), ML models have been employed to predict motor disability scores. This approach involved analysing multiple MRI indexes, including fractional anisotropy and grey matter volumes, to establish the highest classification accuracy for distinguishing between MS patients and healthy controls and predicting motor disability scores in the patients. By providing low-dimensional models with comparable results, these findings open the door to more interpretable ML models, which can significantly enhance our understanding of brain changes in MS and facilitate more accurate treatment planning (Rehák Bučková et al., 2023).

In summary, the integration of ML techniques with MRI brain imaging is rapidly advancing the field of neurology and has transformative implications for disease diagnosis, cost-effective and non-ionising radiation imaging, disease progression prediction, and early detection. As these technologies continue to evolve, they promise to improve the accuracy, accessibility, and effectiveness of diagnosis and treatment in the realm of neurological disorders. The next subchapter explores this ML in application towards sexual dimorphism that will be employed in this doctoral study.

2.7 SYSTEMATIC REVIEW OF SEXUAL DIMORPHISM USING ARTIFICIAL INTELLIGENCE

2.7.1 Introduction

In recent years, the application of AI, particularly through ML techniques, has revolutionized the study of sex differences in the brain. Unlike traditional approaches, which often rely on univariate analyses and predefined hypotheses, ML facilitates the exploration of multivariate patterns in complex neuroimaging datasets. This enables researchers to uncover nuanced distinctions that conventional methods might overlook. Studies employing ML techniques have consistently demonstrated that male and female brains exhibit distinguishable structural and functional features, with classification accuracies in some cases exceeding 90% (Ebel et al., 2023; Sanchis-Segura et al., 2022). These findings underscore ML's transformative potential, highlighting its ability not only as an analytical tool but also as a means to advance our understanding of brain organization and its relationship with biological sex.

A particularly promising avenue in this domain is the use of ML to analyse grey matter features derived from high-resolution structural T1-weighted MRI scans. T1-weighted imaging provides exceptional detail, capturing subtle structural variations that form the basis of ML's pattern-recognition capabilities. By leveraging its ability to process large, high-dimensional datasets, ML can identify small but significant sex-specific differences in grey matter morphology. This combination has proven valuable not only in achieving high classification accuracy but also in uncovering patterns that offer insights into the biological mechanisms underlying neurodevelopmental, psychiatric, and neurological disorders with sex-biased prevalence and progression (Beacher et al., 2012; Collins & Kimura, 1997; Cui et al., 2023; Dai et al., 2015; Salminen et al., 2022; Santana et al., 2014).

The exploration of sexual dimorphism in the brain using AI, however, requires careful ethical consideration. Historically, research into sex differences has been fraught with controversy, with findings sometimes misinterpreted or misused to perpetuate stereotypes. As ML advances this field, it is crucial to ensure that results are communicated responsibly, emphasizing their complexity and avoiding reductionist conclusions. Moreover, the implications of such research extend beyond academic curiosity; the potential to enhance precision medicine, understand sex-specific vulnerabilities to disease, and tailor interventions underscores both the promise, and the responsibility associated with these studies.

This systematic review aims to investigate sex differences in brain structure through the lens of ML, focusing specifically on grey matter features analysed via T1-weighted MRI. By synthesizing recent findings and methodological advances, this review seeks to illuminate the capabilities of ML in addressing the intricate interplay between biological sex and brain structure. In doing so, it aims to provide a nuanced understanding of how AI-driven approaches can contribute to the broader field of neuroscience while addressing the ethical and societal challenges inherent in studying sexual dimorphism.

2.7.2 Methods

2.7.2.1 Protocols and registration

This systematic review was conducted in adherence to the guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, ensuring a comprehensive and transparent approach to the identification, selection, and synthesis of relevant studies. However, it should be noted that the review protocol was not registered in any systematic review database, such as PROSPERO or similar registries. This lack of registration may limit the replicability and traceability of the review process but does not detract from its methodological rigor.

2.7.2.2 Information sources and search strategy

Studies for this systematic review were identified and selected through a structured electronic search and article screening conducted on the PubMed and SCOPUS databases on 22nd November 2024. These databases were specifically chosen for their comprehensive coverage of biomedical and scientific literature, particularly in the domains of brain imaging, sex differences, and machine learning. This strategic selection aimed to maximize the inclusion of high-quality, peer-reviewed research while balancing feasibility and alignment with the study's objectives. To ensure a thorough exploration of relevant studies, a set of carefully curated keywords and text terms were employed. These terms included:

- Sex-related terms: 'sex,' 'gender,' 'dimorphism,' 'disparities,' 'difference.'
- Classification and prediction terms: 'predict,' 'classify,' 'discriminate,' 'distinguish.'
- Brain imaging terms: 'brain,' 'magnetic resonance imaging,' 'MRI.'
- Machine learning terms: 'machine learning,' 'deep learning,' 'classifier.'

Boolean operators (e.g., AND/OR) were used to combine these terms, refining the search to capture studies that intersected these thematic areas. For example, search strings like “(sex OR gender) AND (dimorphism OR predict OR classify OR disparities OR difference OR discriminate OR distinguish) AND (brain) AND (magnetic resonance imaging OR MRI) AND (machine learning OR deep learning)” were employed. The inclusion of exact search strings ensures transparency and reproducibility in the review process, allowing others to replicate the search strategy.

The search encompassed all available literature up to 22nd November 2024, without imposing any date restrictions. This inclusive approach ensured the review captured both foundational studies that have shaped the field and the most recent advancements. The wide

temporal range enhances the robustness of the review, allowing for a comprehensive understanding of historical trends and cutting-edge developments in the application of ML to study sexual dimorphism in brain imaging.

The methodology ensures a systematic and unbiased selection of studies. By leveraging the extensive reach of PubMed and SCOPUS and using a broad, yet focused, set of search terms, this strategy balances specificity with sensitivity. This rigorous approach enhances the credibility and reliability of the systematic review, providing a solid foundation for synthesizing insights at the intersection of brain imaging, sex differences, and machine learning.

2.7.2.3 Eligibility criteria and selection criteria

This systematic review adopted stringent inclusion and exclusion criteria to ensure the relevance, quality, and rigor of the studies analysed. These criteria were designed to focus on high-quality, peer-reviewed research that directly contributes to understanding sex differences in brain structure using structural MRI.

2.7.2.3.1 Inclusion Criteria

Studies were included if they met the following requirements:

- Population: The study focused on in-vivo investigations involving healthy human participants.
- Imaging Modality: The use of structural MRI scans with a high-resolution T1-weighted sequence acquired at a magnetic field strength of 3T.
- Focus: The study analysed sex classification based on grey matter features of the brain.

- Language and Accessibility: Only full-text articles published in English were considered.

2.7.2.3.2 Exclusion Criteria

Studies were excluded if they met any of the following conditions:

- Population: Investigations involving post-mortem samples or non-living populations.
- Imaging Technique: Studies predicting sex using resting-state or task-based functional MRI (fMRI) or diffusion-weighted imaging (DWI) without accompanying T1-weighted imaging.
- Publication Type: Review articles, conference abstracts, or proceedings were excluded to focus on original, peer-reviewed research.
- Language: Non-English studies were excluded due to translation limitations, which might introduce inconsistencies in interpretation.

2.7.2.3.3 Justification for Criteria

- Magnetic Field Strength (3T MRI):

The inclusion of studies using 3T field strength was intentional due to its superior spatial resolution and consistency in signal detection compared to lower-field strengths like 1.5T. This ensures precise measurements of grey matter morphology, which are essential for detecting subtle anatomical differences between sexes. Furthermore, 3T MRI is the current

standard in clinical and research neuroimaging, offering a practical balance between resolution and accessibility.

- T1-Weighted Imaging:

T1-weighted imaging was emphasized because of its ability to provide detailed structural information about grey matter morphology. This makes it particularly suitable for analysing anatomical differences between sexes, which often manifest as subtle variations in grey matter structure.

- Exclusion of Non-English Studies:

While excluding non-English studies may limit the review's scope, it ensures consistency in interpretation and reporting. This approach mitigates the risk of errors introduced by translation and resource constraints, maintaining a uniform standard across all included studies.

- Exclusion of Reviews, Abstracts, and Proceedings:

By excluding secondary sources such as reviews, conference abstracts, and proceedings, the review maintains a focus on original research. This enhances the reliability of the findings by relying on peer-reviewed data that directly addresses the research question.

These criteria were carefully designed to strike a balance between inclusivity and practicality. The focus on studies with consistent methodologies and high-quality data

ensures that the findings provide robust and reliable insights into sex classification based on structural MRI. By concentrating on original, peer-reviewed research, the review underscores its commitment to methodological rigor while addressing the constraints inherent in systematic reviews.

2.7.2.4 Result

2.7.2.4.1 Data extraction

The article selection and screening process followed a systematic and transparent methodology, as outlined in Figure 2.5. This process began with an initial search across two electronic databases, PubMed and SCOPUS, which yielded a total of 73 studies. The following steps were taken to refine this dataset:

- **Removal of Duplicate Entries:** Eighteen duplicate studies were identified and removed, reducing the dataset to 55 unique studies.
- **Initial Screening for Relevance:** A preliminary screening based on titles and abstracts led to the exclusion of 7 irrelevant studies, which did not align with the inclusion criteria or the scope of the review.
- **Full-Text Assessment:** The remaining 48 studies underwent a thorough full-text evaluation to determine their eligibility based on the predefined inclusion and exclusion criteria. Of these, 30 articles were excluded due to lack of focus on grey matter features, use of imaging modalities other than T1-weighted structural MRI and insufficient methodological detail or failure to meet the criteria for population and analysis.
- **Final Selection:** Ultimately, 18 articles were deemed eligible and included in the final analysis.

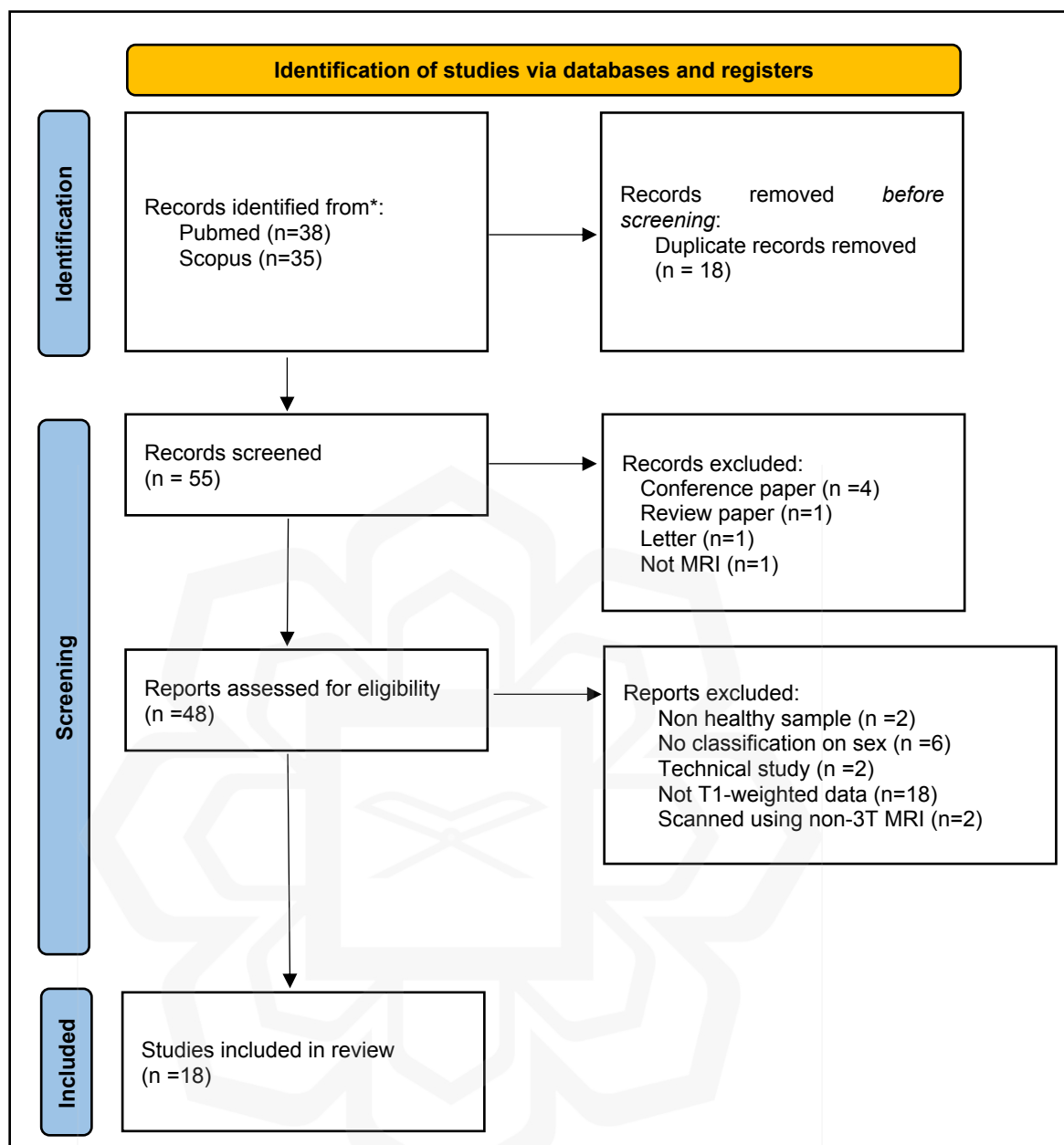


Figure 2.5 PRISMA 2020 flow outlines the systematic process of identifying, screening, and selecting studies for inclusion in the review.

The data extracted from these 18 selected studies have been systematically organized and presented in Table 2.1. The table includes detailed information on:

- Sample Population: Size, demographic details, and sex distribution.
- Age Range: Age distribution of participants to account for developmental and age-related structural differences.
- Morphometric Features: Key grey matter features analysed in each study.
- Machine Learning Methods: Algorithms and techniques applied for sex classification.
- Accuracy: Classification accuracy achieved, highlighting the efficacy of the ML models.

This structured approach ensures that the extracted data provide comprehensive insights into the methodologies and outcomes of the included studies, forming the basis for subsequent analysis and discussion.

Table 2.1 Summary of Studies on Sex Classification Using Grey Matter Morphometric Features and Machine Learning Methods.

Author (year)	Population (Male/Female)	Age range (mean±SD)	Morphometric Features	Classification model	Prediction accuracy/Area under the curve (AUC)
(Besson et al., 2021)	6410 (2893/3517) ^{4,6,10}	6-89 (33.32±17.53)	Inner and outer cortical surfaces	Graph convolutional neural networks (gCNNs)	87.99 % on both surfaces 85.23% inner surface
(Bi et al., 2023)	11700 ¹	9-12	Grey matter data	3D Convolutional neural network (3D CNN)	97.3%
(Brennan et al., 2021)	8325 (4308/4017)	9–10 (119.07±7.48 months)	Cortical Volume Cortical Thickness Cortical Surface Area Sulcal Depth	Support Vector Machine (SVM)	76.1% cortical area 75.20% cortical volume 73.21% SulcD 72.55% cortical thickness 71.37% grey matter intensity 71.01% GWC

			Grey matter intensity White matter intensity Grey-white matter boundary intensity (GWC)		69.38% white matter intensity 86.33% all features
(Dumitru, 2023)	826 (396/430) ²	19-26	Subtraction index (SI) Distance index (DI) Laterality index (LI)	Random Forest (RF)	63% highest for SI using grey matter volume compared to other target measure, 64% highest for DI using grey matter surface area compared to other target measure, 62% highest for LI using grey matter volume compared to other target measure.
(Ebel et al., 2023)	3298 ³ 399 ⁴	21-90 (53) 22-36 (29)	Z-score normalization of grey matter voxels	Convolutional neural network (CNN) Logistic regression	95.78% with LR on SHIP data and 91.8% on HCP data 91.4% with CNN on SHIP data and 85.17% on HCP data

(Feis et al., 2013)	121 (54/67)	20-30 (25±2)	Grey matter segments on T1 weighted, T2 weighted and fractional anisotropy (FA)	Support Vector Machine	88% T1 weighted grey matter segment 85% T2 weighted grey matter segment 83% FA segment 96% multimodal: T1 weighted, T2 weighted, and diffusion weighted (FA)
(Ge et al., 2021)	1063 ⁴ 549 (236/313) ⁵	22-37 17-27	Cortical Volume Cortical Thickness Cortical Folding (gyrification index (GI), fractal dimension (FD), sulcal depth (SulcD))	Linear Discriminant Analysis	80% on cortical thickness, 72% on GI, 71% on cortical volume, 70% on SulcD, 69% on FD. 85% on composite metrics.
(Hu et al., 2019)	876 (385/491) ⁴	22-37	Grey matter data	Multi-Layer 3D Convolution Extreme	98.06%

				Learning Machine (MCN-ELM)	
(Luo et al., 2019)	1113 (507/606) ⁴	22–37	Cortical 3-D Morphology (0.7mm, 1.4 mm and 2.8 mm)	Hierarchical Sparse Representation Classifier (HSRC) Direct sparsity Principal Component Analysis (PCA)	96.77% highest using HSRC on 0.7mm data 94.7% highest using direct sparsity on 1.4mm data 94.52% highest using PCA on 1.4mm data
(Matte Bon et al., 2024)	992 (496/496) ⁴ 1017 (390/627)	22-38 (M: 27.90 ± 3.60, F: 28.98 ± 3.63) 18-30 (M: 22.29 ± 2.86, F: 22.49 ± 2.84)	Volume	Gradient Boosted Trees (GBT)	82.3% on limbic volume 77.6% on non-limbic volume 79.7% on whole brain volume

(Mendes et al., 2021)	580 (428/152) ⁶ 922 (582/ 340) ⁷	6-20 (12.12 ± 3.16) 7.1–19.9 (11.72 ± 2.99)	Grey matter data	3D Convolutional neural network (CNN)	AUC= 0.85 for ADHD-200 AUC=0.82 for ABIDE-II
(Nebli & Rekik, 2020)	698 (308/390)	21-23 (M: 21.6 ± 0.9, F: 21.6 ± 0.8)	Maximum Principal Curvature Cortical Thickness Network Sulcal Depth Network Average Curvature Network	Support Vector Machine	73% sulcal depth network on both hemispheres 70% cortical thickness network on both hemispheres 64% maximum principal curvature on left hemisphere and 66% on right hemisphere 56% on average curvature network on both hemispheres
(Sanchis-Segura et al., 2022)	876 (438/438) ⁴	(28.5±3.4)	Grey matter volume	Linear Discriminant Analysis (LDA) Logistic Regression (LR)	90% highest using SVM, 88.3% using LDA, 88% using MARS, 87.7% using RF, 86.3% using LR.

				Multiple Adaptive Regression Splines (MARS) Random Forest Support Vector Machine	
(Sepehrband et al., 2018)	967 (469/498) ⁸ 682 (360/322) ⁹	8-23 (14.64±3.44) 3-21 (12.29±5.03)	Cortical morphology	Support Vector Machine	83% PNC 77% PING
(L. Wang et al., 2012)	140 (70/70)	18-26 M: (21.2±1.9) F: (20.6±1.6)	Grey matter volume	Support Vector Machine	86.1% grey matter volume 89.1% multimodal: grey matter volume and resting state
(Weber et al., 2022)	1113 (507/606) ⁴	(28.8±3.7)	Grey matter feature	Linear Regression	89.3% highest with resting state pipeline, 84% on grey matter features, 93.3% multimodal: grey matter, white matter, resting state and task evoked fMRI

(X. Yang et al., 2021)	188 (128/60)	0-15 M: (4.1±3.0) F: (3.5±3.0)	Grey matter volume (T1 weighted) data Diffusion tensor imaging (DTI) data	Support Vector Machine	66% on T1 weighted feature 55% on DTI feature 72% on both multimodal features
(Zhang et al., 2020)	290 (135/55)	18-29 M: 22.17 ± 2.49 F: 23.26 ± 2.25	Grey matter volume	Support Vector Machine	94.3% on grey matter volume 96.6 multimodal: grey matter volume, resting state functional connectivity

¹Source from public data: Adolescent Brain Cognitive Development (ABCD)

²Source from public data: Amsterdam Open MRI collection

³Source from public data: Study of Health of Pomerania (SHIP)

⁴Source from public data: Human Connectome Project (HCP)

⁵Source from public data: Southwest University Longitudinal Imaging Multimodal (SHIM)

⁶Source from public data: Autism Brain Imaging Data Exchange II (ABIDE-II)

⁷Source from public data: Attention Deficit Hyperactivity Disorder (ADHD-200)

⁸Source from public data: Philadelphia Neurodevelopmental Cohort (PNC)

⁹Source from public data: Paediatric Imaging, Neurocognition and Genetics (PING)

¹⁰Other Sources: Age-ility, Cambridge Centre for Ageing Neuroscience (CamCan), Consortium for Reliability and Reproducibility (CoRR), Dallas Lifespan Brain Study (DLBS), Brain Genomics Superstruct Project (GSP), Information eXtraction from Images (IXI), MPI-Leipzig Mind Brain Body (MPI-LMBB), Enhanced Nathan Kline Institute – Rockland Sample (NKI-RS), and Southwest University Adult Lifespan Dataset (SALD).

2.7.2.4.2 Grey matter sex classification

This systematic review aimed to evaluate the effectiveness of various ML algorithms in classifying the sex of healthy human brains based on grey matter morphometric features. The findings reveal that classification models consistently achieve high accuracy rates, with results ranging from 56% to 98.06%. The highest accuracy, 98.06%, was achieved using a specialized deep learning technique called the Multi-Layer 3D Convolution Extreme Learning Machine (MCN-ELM), highlighting its superior performance in capturing subtle structural differences in grey matter. Conversely, the lowest accuracy, 56%, was reported for the SVM model, suggesting variability in performance depending on the algorithm employed (Hu et al., 2019; Nebli & Rekik, 2020). These results underscore the potential of advanced ML methods in distinguishing sex-based anatomical features of the brain with high precision.

2.7.2.4.3 Classification models ability

This systematic review categorized studies into two broad groups: those utilizing traditional ML methods and those employing deep learning techniques. The comparative analysis revealed distinct performance trends and methodological preferences across the two paradigms.

Among the 14 studies that employed traditional ML techniques such as SVM, RF, LR, Linear Discriminant Analysis (LDA), and Gradient Boosted Trees (GBT), the highest accuracy achieved was an impressive 96.77%. This exceptional result was attributed to the implementation of an innovative algorithm known as the Hierarchical Sparse Representation Classifier (HSRC). The success of HSRC demonstrates how tailored ML approaches can optimize classification performance by effectively capturing subtle differences in grey matter morphology.

In contrast, the 5 studies utilizing advanced deep learning techniques, particularly the Convolutional Neural Network (CNN) architecture, demonstrated an even greater potential for accuracy, with the best-performing model reaching 98.06% accuracy. This remarkable result highlights the superior capability of CNNs to learn complex patterns in high-dimensional neuroimaging data, such as grey matter features, without the need for extensive manual feature engineering. The exceptional performance of deep learning methods, including CNNs, reinforces their value in pushing the boundaries of brain imaging analysis and sex classification (Hu et al., 2019; Luo et al., 2019).

These findings underscore the strengths and potential of both traditional and deep learning methodologies in analysing brain imaging data. Traditional ML models, when paired with innovative techniques like HSRC, can achieve competitive results, while DL approaches provide unparalleled accuracy by leveraging their capacity for automatic feature extraction and modelling of non-linear patterns. This comparison illustrates the diverse landscape of ML in neuroscience, where both paradigms offer unique advantages depending on the context and requirements of the study.

Among the 14 studies employing ML techniques to investigate sex differences in the brain, SVM emerged as the most popular method, used in 8 studies. One notable study, conducted by Zhang et al. in 2020, achieved the highest accuracy of 94.3% among the SVM-based studies by leveraging grey matter volume as the primary morphometric feature. This highlights SVM's effectiveness in modelling structural differences when appropriate features are selected.

The remaining studies explored a diverse array of ML approaches, including Linear Regression, LR, RF, Multiple Adaptive Regression Splines (MARS), HSRC, Direct Sparsity, Principal Component Analysis (PCA), GBT, and LDA. These varied methodologies reflect the adaptability of ML to different neuroimaging datasets and analytical goals. A wide range of classification accuracies was observed across these techniques, spanning from 62% to 96.77%. The lowest accuracy was reported for the RF method, indicating its limited effectiveness in capturing nuanced structural differences in this context. In contrast, the highest accuracy of 96.77% was achieved using the HSRC

model, showcasing the potential of innovative and specialized algorithms in optimizing classification outcomes.

This variation in accuracy underscores the importance of selecting the most suitable ML algorithm for a given study, as the effectiveness of each method can depend significantly on the dataset, feature selection, and preprocessing strategies. These findings highlight the competitive performance of SVM in this domain, while also emphasizing the need for continued exploration of advanced methods, such as HSRC, to further enhance the accuracy and robustness of sex classification in brain imaging studies (Dumitru, 2023; Ge et al., 2021; Luo et al., 2019; Sanchis-Segura et al., 2022; Weber et al., 2022).

In a comprehensive comparative study evaluating five ML algorithms—LDA, LR, MARS, RF, and SVM—the performance of these methods in classifying brain sex was assessed. The study included a robust dataset of 876 volunteers, matched for sex and age, ensuring a balanced analysis. Among the algorithms, SVM achieved the highest accuracy of 90% when applied to grey matter volume data without correction for total intracranial volume (TIV). The other methods followed closely, with LDA achieving 88.3%, MARS with 88%, RF with 87.7%, and LR with 86.3% (Sanchis-Segura et al., 2022).

In a separate study conducted by Ebel et al. in 2023, a direct comparison was made between LR and CNN. Surprisingly, LR outperformed CNN, achieving a higher accuracy of 95.78%. This study utilized z-score normalization of grey matter voxel data and drew on a large public dataset, the Study of Health in Pomerania (SHIP), underscoring the impact of feature preprocessing and dataset characteristics on algorithm performance.

These findings highlight the diverse efficacy of ML methodologies in discerning sex differences in brain imaging studies. While advanced methods like CNN often excel due to their ability to capture complex patterns, simpler algorithms such as LR can outperform them in certain contexts when paired with effective preprocessing techniques and well-structured data. This variability underscores the importance of tailoring ML approaches to the specific characteristics of the dataset and the research question.

2.7.2.4.4 Effect of morphological features

The effectiveness and precision of ML models in brain imaging studies are significantly influenced by the choice of morphological features. This systematic review emphasized features extracted from T1-weighted MRI scans, with a particular focus on grey matter segment data. Among the five studies reviewed that utilized grey matter volume as the central morphological feature (Matte Bon et al., 2024; Sanchis-Segura et al., 2022; L. Wang et al., 2012; X. Yang et al., 2021; Zhang et al., 2020), varying levels of classification accuracy were reported. Zhang et al. (2020) achieved the highest accuracy of 94.3%, demonstrating the robustness of SVM in analysing high-dimensional grey matter data. Similarly, Sanchis-Segura et al. (2022), using a comparative approach across multiple ML algorithms, reported a peak accuracy of 90%, also employing SVM. Wang et al. (2012) achieved an accuracy of 86.1%, reflecting consistent performance despite being an earlier study. In contrast, Yang et al. (2021) reported the lowest accuracy of 66%, which may be attributed to differences in data quality, feature extraction, or model optimization. Matte Bon et al. (2024) deviated from the common use of SVM, applying GBT to analyse limbic and non-limbic grey matter volumes. Their study achieved an accuracy of 82.3% for limbic volumes, a region exhibiting pronounced sexual dimorphism, but only 77.6% for non-limbic volumes, underscoring the importance of regional specificity in feature selection. Across these studies, SVM emerged as the dominant and effective method, employed in four out of the five investigations, due to its ability to handle high-dimensional data and achieve high classification accuracy. The reported accuracies, ranging from 66% to 94.3%, highlight the critical role of careful feature selection and algorithm choice in determining model performance, with region-specific features and advanced algorithms proving particularly effective for distinguishing sex differences in brain morphology.

Six studies investigated sex classification using global grey matter data, segments, or intensity features, employing a variety of ML and DL techniques (Bi et al., 2023; Brennan et al., 2021; Feis et al., 2013; Hu et al., 2019; Mendes et al., 2021; Weber et al., 2022). Among these, Hu et al. (2019) achieved the highest accuracy, an exceptional 98.06%, using the MCN-ELM, a specialized deep learning method that demonstrates the

transformative potential of advanced neural networks in grey matter analysis. Close behind, Bi et al. (2023) achieved an impressive 97.3% accuracy with a CNN, further underscoring the capabilities of deep learning for high-dimensional data analysis. Other studies demonstrated varying levels of performance based on their methodological choices. Feis et al. (2013) reported an accuracy of 88%, reflecting solid performance but lower than DL approaches. Brennan et al. (2021), employing the more traditional SVM, achieved a moderate accuracy of 71.37%, highlighting the limitations of traditional ML when compared to deep learning in this context. Similarly, Weber et al. (2022) used Linear Regression, achieving an accuracy of 84%, a result that demonstrates reliability but lacks the competitive edge of deep learning methods. Finally, Mendes et al. (2021) utilized a CNN-based deep learning approach, reporting an AUC of 0.85, reflecting good predictive ability.

Five studies examined the complexities of cortical structure, focusing on metrics such as cortical 3D morphology, cortical thickness, cortical surface area, and cortical folding characteristics, including the gyrification index (GI), sulcal depth (SulcD), and FD (Besson et al., 2021; Brennan et al., 2021; Ge et al., 2021; Luo et al., 2019; Sepehrband et al., 2018). These metrics provide valuable insights into cortical anatomy and its potential role in distinguishing sex-based differences in brain structure. Among the studies, Luo et al. (2019) reported the highest accuracy of 96.77%, achieved using cortical 3D morphology measurements analysed with their proprietary ML algorithm, the HSRC. This result highlights the efficacy of specialized algorithms in capturing intricate cortical features for sex classification. Ge et al. (2021) investigated five distinct cortical features using LDA and observed varied accuracies across features. The highest accuracy of 80% was achieved with cortical thickness, followed by 72% for GI, 71% for cortical volume, 70% for SulcD, and 69% for FD. These findings indicate that cortical thickness is the most robust metric for distinguishing between sexes, while other features contribute to varying extents.

Three studies in this systematic review explored modified indices as features for sex classification (Dumitru, 2023; Ebel et al., 2023; Nebli & Rekik, 2020). Dumitru (2023) investigated brain asymmetry through three indices: Subtraction Index (SI), Distance Index (DI), and Laterality Index (LI), achieving accuracies of 63%, 64%, and 62%, respectively.

These results highlight the modest performance of asymmetry indices in distinguishing sex differences in brain structure. In contrast, Ebel et al. (2023) utilized z-score normalization of grey matter voxel data and achieved an impressive accuracy of 95.78% using LR. This study underscores the potential of feature normalization and logistic regression as effective approaches for analysing grey matter data in sex classification tasks. Nebli and Rekik (2020) examined a variety of cortical network features, including maximum principal curvature, cortical thickness network, sulcal depth network, and average curvature network, reporting accuracies of 66%, 70%, 73%, and 56%, respectively. These findings demonstrate the varying discriminative power of cortical network features, with the sulcal depth network achieving the highest accuracy and the average curvature network yielding the lowest.

Seven studies investigated the accuracy of distinguishing sex by combining multiple morphological and functional features, demonstrating superior performance compared to using individual features alone (Brennan et al., 2021; Feis et al., 2013; Ge et al., 2021; L. Wang et al., 2012; Weber et al., 2022; C. C. Yang et al., 2023; Zhang et al., 2020). Brennan et al. (2021) observed a significant improvement in classification accuracy, increasing from a range of 69–76% with individual features to 86.33% by integrating a diverse set of morphological features. These included cortical area, cortical thickness, cortical volume, SulcD, grey matter intensity, white matter intensity, and grey-white matter boundary intensity (GWC). This improvement underscores the synergistic potential of combining features that capture different aspects of brain morphology. Similarly, Ge et al. (2021) demonstrated an enhancement in accuracy from 80% (using cortical thickness alone) to 85% when integrating multiple features, including cortical thickness, cortical volume, gyrification index, sulcal depth, and FD. This study highlights how the combination of complementary metrics provides a more comprehensive representation of brain structure, thereby improving the model's ability to distinguish sex-based differences. These findings collectively emphasize the advantages of multi-feature integration in sex classification tasks. By leveraging diverse morphological and functional attributes, these studies illustrate that combining features allows ML models to capture a broader spectrum of structural variations, leading to enhanced accuracy and robustness in classification outcomes.

Five studies achieved enhanced accuracy by integrating multiple morphological and functional features derived from various MRI sequences, including T2-weighted, diffusion-weighted, resting-state fMRI, and task-evoked fMRI. This multi-modal approach leveraged the strengths of diverse imaging techniques to provide a more comprehensive representation of brain structure and function, resulting in notable improvements in sex classification accuracy. The earliest study, Wang et al. (2012), demonstrated an increase in accuracy to 89.1% by combining grey matter volume with resting-state fMRI features, outperforming the 86.1% accuracy achieved using grey matter volume alone. This highlights the complementary value of integrating structural and functional data. Similarly, Feis et al. (2013) achieved a near-perfect accuracy of 96% by combining features from three MRI sequences: T1-weighted (88%), T2-weighted (85%), and diffusion-weighted sequences (83%). The synergy between these modalities underscores the importance of incorporating diverse data types to capture sex-based differences in both structure and connectivity. Recent investigations have further demonstrated the potential of multi-modal integration. Weber et al. (2022) reported an accuracy of 93.3%, and Zhang et al. (2020) achieved an even higher accuracy of 96.6%, both by combining features from grey matter, white matter, resting-state fMRI, and task-evoked fMRI. These studies illustrate how incorporating functional imaging data alongside structural features can significantly enhance model performance by providing insights into both the physical and dynamic aspects of brain differences. These findings collectively highlight the substantial benefits of integrating features from multiple MRI modalities in improving the precision of sex classification models. By combining complementary structural and functional attributes, these studies emphasize the power of multi-modal approaches in capturing the complex interplay between anatomical and functional differences, resulting in more robust and accurate classification outcomes.

An essential aspect of understanding sex classification in brain imaging is identifying specific brain regions that contribute to accuracy, potentially highlighting the hallmark regions of sexual dimorphism. Three studies in this review reported classification accuracy in relation to specific brain regions, offering valuable insights into the regional specificity of sex-based differences. In the most recent study, Matte Bon et al. (2024)

analysed the discriminative power of various brain regions, reporting an accuracy of 82.3% for limbic volume, 77.6% for non-limbic volume, and 79.7% for the whole brain volume. These results emphasize the importance of the limbic system, which includes structures like the hippocampus and amygdala, in distinguishing sex differences. Another study by Ebel et al. (2023) provided a detailed breakdown of regional contributions using logistic regression. The whole brain achieved the highest accuracy, with an AUC of 0.98, demonstrating its overall utility in sex classification. This was followed by specific regions such as the cerebellum (AUC 0.95), thalamus (0.88), frontal pole (0.86), amygdala and hippocampus (0.84), occipital lobe (0.84), and basal ganglia and putamen (0.82). These findings underline the widespread distribution of sex differences across various brain regions while highlighting the cerebellum and thalamus as particularly discriminative. In a separate investigation, Luo et al. (2019) focused on the spatial distribution of discriminative features, finding that regions in the frontal lobe were the most predictive of sex, achieving an accuracy of 87.87%. In contrast, the temporal gyrus exhibited the lowest predictive accuracy at 62.89%, indicating that not all regions contribute equally to classification models. These studies collectively underscore the importance of regional specificity in sex classification tasks. While the whole brain consistently provides the highest overall accuracy, specific regions such as the frontal lobe, cerebellum, and limbic system stand out for their strong discriminative power. These findings offer a nuanced understanding of the anatomical basis of sexual dimorphism in the brain and provide a foundation for future research aimed at unravelling the biological mechanisms underlying these differences.

2.7.2.4.5 Age group difference

Considering the well-documented age effects on human brain development, this systematic review underscores the critical role of age in evaluating the accuracy of ML models for discerning sex differences in brain structure (Dumitru, 2023; Witelson et al., 2006). Studies included in this review span a range of age groups, revealing distinct patterns in

classification accuracy and emphasizing the importance of tailoring methodologies to developmental stages.

- Children and Adolescents (<20 years old)

Four studies focused on children and adolescents under the age of 20, highlighting the potential of ML in this age group (Bi et al., 2023; Brennan et al., 2021; Mendes et al., 2021; X. Yang et al., 2021). Among these, the highest accuracy of 97.3% was reported by Bi et al. (2023) in a large sample of approximately 11,000 participants aged 9 to 12 years, using a deep learning algorithm. This exceptional performance underscores the utility of advanced models in analysing the rapidly developing brains of children and adolescents. Other studies in this group reported moderate accuracies, reflecting variability based on methodological differences and sample characteristics.

- Young Adults (20–37 years old)

For young adults, aged approximately 20 to 37 years, 12 studies predominantly utilized data from the Human Connectome Project (HCP), a rich resource for neuroimaging research (Dumitru, 2023; Ebel et al., 2023; Feis et al., 2013; Ge et al., 2021; Hu et al., 2019; Luo et al., 2019; Matte Bon et al., 2024; Nebli & Rekik, 2020; Sanchis-Segura et al., 2022; L. Wang et al., 2012; Weber et al., 2022; Zhang et al., 2020). The highest accuracy in this group, 98.06%, was achieved by Hu, Luo, and Zhao (2019) using a deep learning approach. This result reflects the robustness of ML in capturing subtle sex differences in fully matured adult brains. The large number of studies in this group highlights the popularity of young adult populations in neuroimaging research, given their relative neurodevelopmental stability and the availability of high-quality datasets like HCP.

- Older Adults (21–90 years old)

In contrast, only one study specifically examined older adults, aged 21 to 90 years (Ebel et al., 2023). This study achieved an impressive accuracy of 95.78%, using logistic regression with z-score normalization of grey matter voxels. The limited number of studies in this age group reflects a gap in the literature, despite the importance of understanding sex differences in aging populations, where brain structure and function are influenced by age-related neurodegenerative changes.

2.7.3 Discussion

This systematic review aimed to evaluate the effectiveness and accuracy of ML techniques in determining the sex of healthy human brains by leveraging grey matter morphometric features. The analysis revealed strong evidence that sex classification could be reliably achieved using a variety of ML algorithms applied to diverse T1-weighted morphological data across different age groups. These findings underscore the potential of ML models to discern biological sex based on distinct neural characteristics, supporting the notion that male and female brains exhibit distinguishable patterns in their structural morphology (Del Mauro et al., 2022; Ruigrok et al., 2014). Notably, the study reporting the lowest accuracy of 56% highlighted the critical role of feature selection, as it relied on the unique approach of quantifying cortical morphological connectivity, which likely contributed to its comparatively lower performance (Nebli and Rekik 2020). This variability emphasizes the importance of feature-specific considerations in optimizing classification accuracy and broadens the understanding of how structural connectivity might influence ML outcomes in this context.

The classification models examined in this systematic review consistently showcased high accuracy in distinguishing sex based on structural brain features. The

evaluation incorporated a variety of ML algorithms, an essential consideration given the potential variability in outcomes arising from the distinct internal mechanisms of each algorithm (Sasikala et al., 2017). This diversity not only facilitated comparative analyses but also highlighted the potential for integrating outcomes from multiple algorithms to yield more robust and generalizable conclusions. Such a multifaceted approach strengthens the reliability and applicability of sex classification models using structural brain MRI data, offering deeper insights into the nuanced neurobiological differences between sexes.

Among the reviewed studies, a predominant reliance on SVM was observed. SVM are widely regarded as one of the most effective ML algorithms, particularly for their exceptional predictive accuracy (Guo et al., 2023; Kim, 2004). This aligns with findings from comparative studies that have established SVMs' superior performance over other methods, such as LDA, LR, MARS, and RF (Sanchis-Segura et al., 2022). These results underscore SVMs' utility in sex classification tasks and highlight their prominence as a benchmark for evaluating the performance of other algorithms. Additionally, the comprehensive inclusion of various algorithms facilitates a holistic understanding of their relative strengths and limitations, thereby advancing the development of highly accurate and reliable classification models.

The performance of ML models in sex classification using structural brain MRI data varied substantially across the studies reviewed, emphasizing the influence of both model selection and methodological approaches. Traditional ML models, including SVM, LR, RF, and LDA, demonstrated moderate to high accuracy levels, contingent on the datasets and features utilized. For instance, Sanchis-Segura et al. (2022) identified SVM as the most effective traditional model, achieving an accuracy of 90%, while LR followed closely with 86.3%. Similarly, Zhang et al. (2020) reported an impressive SVM accuracy of 94.3% when employing grey matter volume as input, further enhanced to 96.6% through multimodal data integration.

However, some studies revealed the limitations of feature-specific methodologies. For example, Nebli and Rekik (2020) observed significantly lower performance, with SVM achieving only 56% accuracy when applied to average curvature network features. This discrepancy highlights the variability in model performance based on the chosen features

and underscores the importance of feature selection and preprocessing in optimizing traditional ML approaches.

In contrast, deep learning models consistently outperformed traditional methods, demonstrating their capacity to achieve state-of-the-art accuracy. For example, Hu, Luo, and Zhao (2019) achieved the highest reported accuracy of 98.06% using the MCN-ELM. Similarly, Bi et al. (2023) reported an accuracy of 97.3% with a 3D CNN. These advanced architectures excel in their ability to autonomously learn complex patterns in neuroimaging data, a critical advantage over traditional models that rely heavily on predefined features and feature engineering.

These findings illustrate the evolving landscape of ML in neuroimaging. While traditional models provide reliable baselines and remain competitive with appropriate feature engineering and preprocessing, deep learning models represent the cutting edge, offering unparalleled accuracy and versatility. This dichotomy highlights the complementary roles of these approaches, with traditional methods serving as benchmarks and deep learning architectures driving innovation and precision in sex classification from structural brain MRI data.

The selection of morphological features plays a pivotal role in determining the performance of ML models in sex classification. Features such as grey matter volume, cortical thickness, and regional intensity have shown varying levels of predictive efficacy across different studies. A recurring trend observed in the review is that combining multiple morphological features often leads to improved model accuracy. This suggests that integrating diverse structural markers enhances the robustness and generalizability of classification models by capturing a broader spectrum of neuroanatomical variation.

Despite these advancements, this review also highlights a significant gap in the exploration of specific brain regions that contribute to classification accuracy. While most studies focus on global morphological characteristics, fewer have delved into the regional contributions that drive classification performance. Notably, regions such as the frontal lobe, cerebellum, limbic system, and thalamus consistently emerged as critical contributors to accurate classification. These findings align with established literature on

neuroanatomical sex differences, which frequently associate these regions with structural and functional distinctions between males and females (Ebel et al., 2023; Luo et al., 2019; Matte Bon et al., 2024).

The consistent identification of these key brain regions underscores their importance in sex classification models and supports their inclusion in future research. Incorporating targeted analyses of these regions, alongside global morphological features, may further refine classification models and deepen understanding of the neurobiological underpinnings of sex differences. This integrative approach could pave the way for more nuanced and precise applications of ML in neuroimaging.

The accuracy of ML models for sex classification using brain MRI data is influenced by both the architecture of the model and the size and diversity of the study population. DL models, renowned for their ability to autonomously learn complex patterns, have demonstrated remarkable performance even with limited datasets. For instance, Hu, Luo, and Zhao (2019) achieved a groundbreaking accuracy of 98.06% using the MCN-ELM on a dataset of 876 participants. While this underscores the capacity of deep learning models to generalize effectively, larger datasets could further validate these outcomes and enhance model reliability by mitigating potential biases introduced by small sample sizes.

In contrast, Bi et al. (2023) achieved a similarly impressive accuracy of 97.3% using a 3D CNN applied to a significantly larger dataset of 11,700 adolescents. This highlights the critical role of large-scale datasets in improving model robustness, minimizing overfitting, and capturing broader population variability. The enhanced performance of models trained on extensive datasets demonstrates their superior ability to reflect real-world diversity and neuroanatomical variability across different demographic groups.

Traditional ML models, such as SVM, also exhibited notable performance variations tied to population size and sample diversity. Zhang et al. (2020) achieved an SVM accuracy of 94.3% using a small dataset of 290 participants, a result that, while impressive, raises concerns about overfitting and the limited generalizability of findings. Comparatively, Sanchis-Segura et al. (2022) reported a peak SVM accuracy of 90% using a balanced dataset of 876 participants. This finding highlights the importance of sample

balance for model performance, yet it also underscores the limitations of smaller datasets in capturing the full spectrum of neuroimaging variability.

The largest dataset reviewed, comprising 32,983 participants, was used by Ebel et al. (2023), who achieved high accuracies with LR (95.78%) and CNN (91.4%). While these results underscore the advantages of large datasets in enhancing model robustness and reducing overfitting, the reliance on public datasets raises concerns about potential population biases that might limit the generalizability of the models to underrepresented groups.

These comparisons reveal that while DL models typically outperform traditional approaches, their full potential is realized when trained on large, diverse datasets. The findings emphasize the symbiotic relationship between population size and model performance, suggesting that future research should prioritize both advanced model architectures and expansive, demographically varied datasets to achieve optimal accuracy and generalizability in sex classification tasks using brain MRI data.

The methodological rigor across the reviewed studies exhibited considerable variation, reflecting disparities in dataset size, diversity, and preprocessing practices. While some studies utilized large, heterogeneous datasets and implemented rigorous preprocessing pipelines to enhance data quality and model performance, others were constrained by smaller, more homogeneous samples. This inconsistency underscores the urgent need for standardization in preprocessing and feature extraction methodologies. Standardization would not only ensure reproducibility and facilitate cross-study comparisons but also improve the generalizability of findings across diverse populations and study conditions.

A notable limitation observed in the reviewed literature was the predominant focus on younger age groups, typically ranging from 20 to 37 years. This narrow age range leaves a significant gap in understanding how age-related morphological changes in the brain influence sex classification accuracy. Older populations, who experience more pronounced structural changes due to aging, were underrepresented. Including such populations in future research could illuminate how age-related variations affect the performance of ML

models and may reveal additional morphological features or patterns critical for classification accuracy in older age groups.

By addressing these methodological inconsistencies and expanding demographic representation, future studies can provide more comprehensive insights into the interplay between brain morphology, age, and sex classification. Such advancements would contribute to developing more robust, equitable, and universally applicable ML models for neuroimaging-based sex classification.

2.7.4 Limitation

A key limitation of this systematic review is the predominant reliance on similar public datasets across the included studies, which introduces the potential for population bias in the findings. While these datasets offer consistency and accessibility, their repetitive use may limit the diversity of demographic and neuroanatomical characteristics represented, thus constraining the generalizability of the results. Nonetheless, many studies mitigated this limitation by supplementing their analyses with additional datasets, thereby enhancing statistical power and providing a broader foundation for their conclusions.

Another notable limitation is the restriction to studies published in English, which inherently excludes research published in other languages. This language exclusivity may lead to the omission of valuable insights and innovative methodologies developed in non-English-speaking contexts, thereby limiting the comprehensiveness of the review. Such a restriction could skew the overall findings, particularly in fields where regional differences in study populations or analytical approaches might provide unique perspectives.

To address this limitation in future reviews, expanding the inclusion criteria to encompass studies published in other languages would be a critical step. This could be achieved using professional translation services or by collaborating with multilingual researchers who can accurately interpret and analyse findings from non-English sources.

Such an approach would ensure a more diverse and inclusive representation of global research, ultimately improving the robustness, applicability, and cross-cultural relevance of the findings.

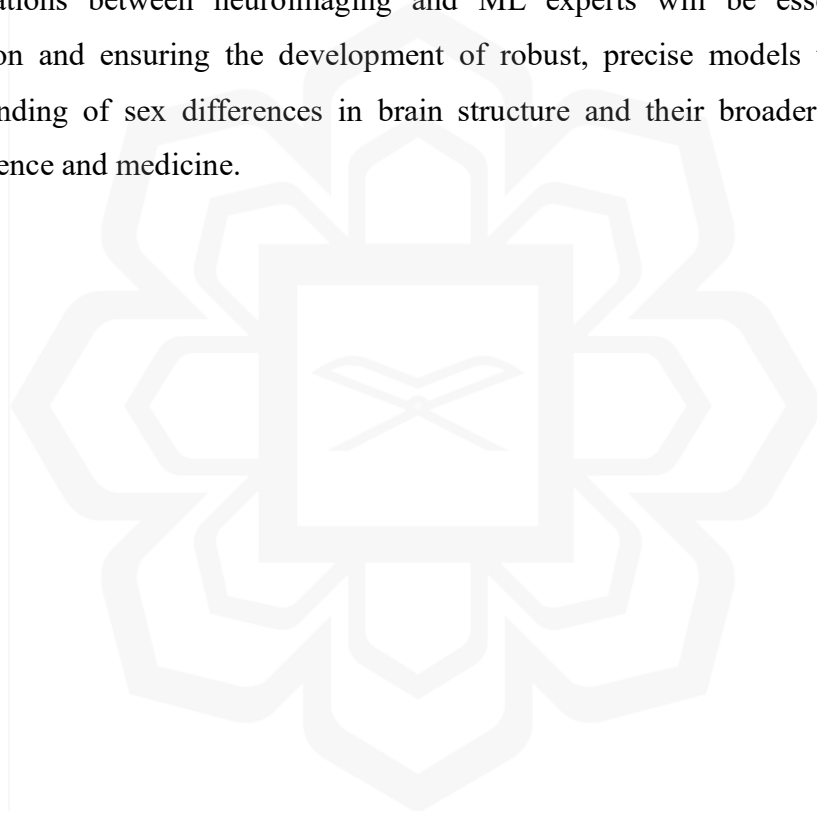
These limitations must be carefully considered when interpreting the scope and generalizability of the conclusions presented in this review. Acknowledging and addressing these gaps in future research efforts will contribute to a more equitable and comprehensive understanding of the field.

2.7.5 Conclusions

In conclusion, this systematic review explored the advancements and methodologies in sex classification using structural brain MRI data and ML techniques. The studies reviewed employed a wide range of ML algorithms and morphometric features derived primarily from grey matter, yielding high classification accuracies, with the highest reaching 98.06%. The findings highlighted the value of combining multiple morphological and functional features, which frequently resulted in enhanced accuracy, emphasizing the critical role of effective feature selection and integration in these models. Furthermore, age-specific analyses provided insights into the performance of these models across various age groups, though the representation of older populations remains a significant gap in the current research.

The review also identified certain limitations, such as the reliance on similar public datasets, which could introduce population bias, and the exclusion of studies published in languages other than English, potentially omitting valuable contributions from non-English-speaking researchers. These factors limit the generalizability of the findings and highlight areas for improvement in future research design. Despite these challenges, this review offers a comprehensive synthesis of existing knowledge, contributing valuable insights into the application of ML for sex classification in structural brain MRI studies.

Future research should aim to address these limitations by integrating more diverse datasets that include underrepresented age groups, ethnicities, and populations, thereby enhancing the generalizability and inclusivity of the models. Expanding the scope of analysis to incorporate multimodal imaging data, such as functional MRI or diffusion tensor imaging, could further refine classification accuracy and provide deeper insights into the interplay between brain structure and function. Clinicians, researchers, and policymakers should leverage these findings to develop diagnostic tools that are not only accurate but also representative of diverse populations. Finally, fostering interdisciplinary collaborations between neuroimaging and ML experts will be essential in driving innovation and ensuring the development of robust, precise models that advance our understanding of sex differences in brain structure and their broader implications for neuroscience and medicine.



CHAPTER THREE

METHODOLOGY

3.1 INTRODUCTION

This chapter details the methodological framework employed in this research, detailing the study design, ethical consideration, neuroimaging acquisition protocols, and the preprocessing procedures applied to the data. These elements lay the groundwork for the investigation. Then, specific methodologies utilized in this study - VBM, VOI analyses, and ML classification - will each be covered in detail later in this chapter, highlighting their specific applications and contributions to addressing the research questions.

3.2 DEMOGRAPHIC DATA AND SUBJECTS CHARACTERISTICS

3.2.1 Study Design

This study utilized a retrospective dataset consisting of T1-weighted MRI scans from a carefully selected cohort of healthy young male and female adults, aged between 20 to 25 years. The meticulous selection of participants, coupled with the strategic division into Huffaz and non-Huffaz groups, allowed for a focused investigation into the potential impact of cognitive training on brain structure, particularly in the context of sex differences.

3.2.2 Inclusion and Exclusion Criteria

The data selection was conducted based on stringent inclusion and exclusion criteria to ensure the homogeneity and reliability of the sample. Participants were strongly right-handed, as to ensure uniform patterns of brain lateralization (Budisavljevic et al., 2020). Additionally, participants had no history of head injury, were free from any medical illnesses. Health information was self-reported by the participants and corroborated by further evaluation by a senior radiologist, Assoc. Prof. Dr. Radhiana Hassan to maintain the study's stringent standards. The inclusion of only those who met these strict criteria was essential for achieving a homogenous sample, which is necessary to ensure that the statistical analyses would accurately reflect the effects of the cognitive training on brain structure. This methodological rigor is crucial for drawing valid conclusions about the influence of sustained cognitive practices, such as those experienced by Huffaz, on sexual dimorphism in brain structure.

3.2.3 Division of Participants: Huffaz and Non-Huffaz Groups

To investigate the potential impact of cognitive practices on brain structure, the cohort was strategically divided into two distinct groups: Huffaz and non-Huffaz. The Huffaz group was composed of individuals who had recently graduated (within four years) from the Tahfiz Certificate Program at Darul Quran-IIUM, a rigorous 18-month program dedicated to the memorization of the entire Quran. These individuals were selected to explore the potential effects of sustained and intensive cognitive training on brain morphology. Additionally, participants in the Huffaz group actively engaged in recall memorization classes, known as muraja'ah, which required them to continuously review and reinforce their memorized material. This ongoing engagement was a critical criterion to maintain homogeneity in brain plasticity within the Huffaz group, thereby allowing for a more precise analysis of the potential neuroanatomical effects of intensive memorization.

In contrast, the non-Huffaz group consisted of ordinary undergraduate students who had no exposure to Quran memorization exercises. This group served as a control to help delineate the specific effects of the cognitive training experienced by the Huffaz group. Both groups were comprised of students from the International Islamic University Malaysia (IIUM) Kuantan Campus. Participation was voluntary, and all volunteers were fully informed about the study's objectives before providing consent. The voluntary nature of the recruitment and the informed consent process adhered strictly to the ethical standards outlined in the Declaration of Helsinki.

The final sample comprised a total of 47 participants with 19 males and 28 females, with a mean age of 22.55 years ($SD = 1.472$). Within this group, 23 individuals were Huffaz (12 females and 11 males), and 24 were non-Huffaz (16 females and 8 males). Detailed demographic data is provided in Table 3.1 and illustrated in Figure 3.1. The bar chart illustrates the number of Huffaz (dark blue) and non-Huffaz (light blue) among males and females. Females have a higher count of Huffaz (16) compared to males (8), while the number of non-Huffaz is also slightly higher among females (12) than males (11).

Table 3.1 Demographic characteristics of the study participants.

Sex	N	N (Huffaz, non-Huffaz)	Age (years), mean $\pm$ SD
Male	19	11,8	22.47 $\pm$ 1.22
Female	28	12,16	22.64 $\pm$ 1.57

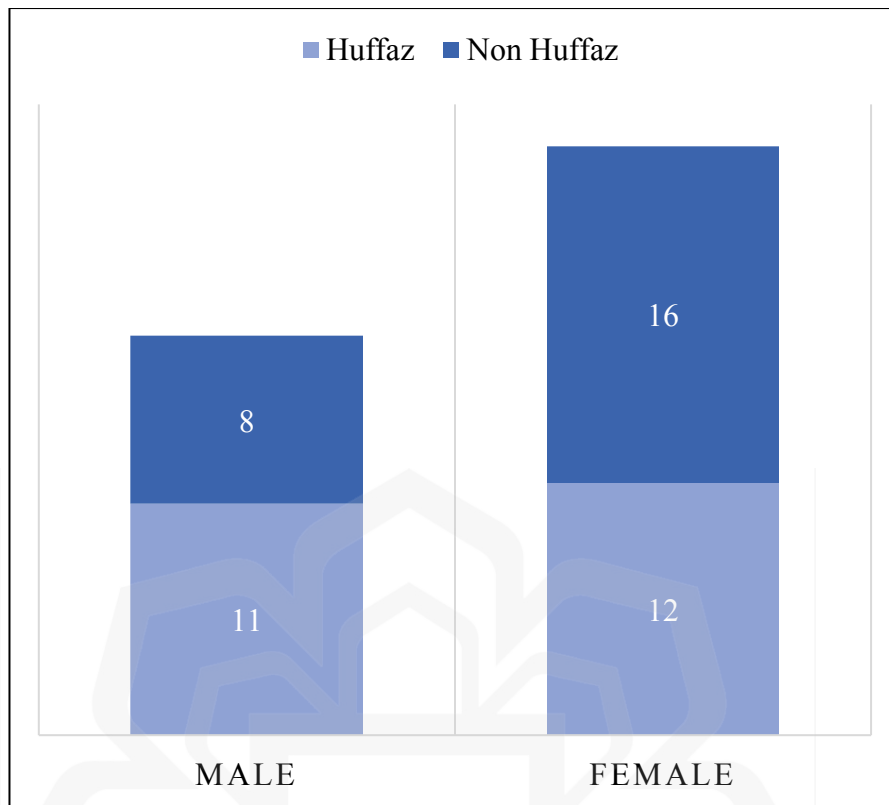


Figure 3.1 Distribution of Huffaz and Non-Huffaz by Sex.

3.3 ETHICAL APPROVAL

This study was conducted in full accordance with ethical principles and guidelines for research involving human subjects. Ethical approval was granted by the IIUM Research Ethics Committee (IREC) under reference number IREC: IIUM/504/14/11/2/IREC 2024-040, dated 26 March 2024. The approval letter from the IREC committee is included in the APPENDIX I: ETHICAL APPROVAL section of this thesis for reference.

Key ethical considerations addressed in this study include:

- **Informed Consent:** All participants were provided with detailed information about the study's purpose, procedures, potential risks and benefits, and their right to withdraw at any time without penalty. Written informed consent was obtained from all participants before their involvement in the study.
- **Confidentiality and Anonymity:** All collected data was handled with strict confidentiality. Participant identities were anonymized, and data was stored securely to protect privacy.
- **Data Security and Integrity:** Data management and analysis adhered to rigorous standards to ensure data integrity and prevent unauthorized access or misuse.

3.4 IMAGE ACQUISITION

High-resolution T1-weighted structural MRI data were obtained for each participant using a state-of-the-art 3 Tesla Magnetom Siemens scanner (Erlangen, Germany), situated at the Department of Radiology, Sultan Ahmad Shah Medical Centre@IIUM in Kuantan, Pahang. For head scanning, this advanced scanner was equipped with a mobile head and neck coil featuring 16 channels, which provided enhanced signal sensitivity and uniformity across the entire field of view, which is essential for achieving high-quality images with detailed anatomical precision.

To achieve consistent and high-quality imaging across all participants, a standardized 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence was employed. This sequence is widely recognized for its ability to produce detailed images of brain anatomy, allowing for precise measurements of cortical and subcortical structures. The following acquisition parameters were meticulously selected to balance image clarity and acquisition efficiency: repetition time (TR) = 1880 ms, echo time (TE) = 3 ms,

acquisition time (TA) = 4.23 minutes, field of view (FoV) = 250 mm in the read direction, and slice thickness = 1.0 mm with single averaging.

The resulting isotropic voxel size of 1.0 mm x 1.0 mm x 1.0 mm was chosen to ensure high spatial resolution, allowing for the accurate delineation of fine anatomical details. This high resolution is particularly important for studies involving VBM and other advanced neuroimaging analyses, as it enhances the ability to detect subtle differences in brain structure. Additionally, the use of single averaging helped maintain data integrity by reducing noise, further contributing to the reliability of the acquired images.

This meticulous image acquisition protocol was designed to provide the highest quality data possible, thereby enabling precise and reliable investigation into the structural differences between the Huffaz and non-Huffaz groups, and between males and females within these groups.

3.5 IMAGE PRE-PROCESSING

All MRI images were initially stored in raw Digital Imaging and Communications in Medicine (DICOM) format. To facilitate further analysis using advanced neuroimaging software, the first step involved converting these DICOM images into the Neuroimaging Informatics Technology Initiative (NIfTI) format. This conversion was essential because the statistical parametric mapping software (SPM12), along with MATLAB, requires images to be in NIfTI format for detailed analysis. Without this conversion, the images could not be properly processed or analysed using the tools available in SPM12 and MATLAB.

Once converted to NIfTI format, the images were pre-processed using the CAT12 toolbox (Gaser et al., 2022), an extension of SPM12 software, which operates within the MATLAB R2023a (The MathWorks, Sherborn, MA) platform. Throughout the entire pre-processing pipeline, the CAT12 toolbox, was employed to enhance the accuracy and

robustness of the segmentation process and other preprocessing steps than the standard SPM12. CAT12 offers an advanced and comprehensive approach to preprocessing, integrating several sophisticated techniques that improve the reliability of the data for subsequent analysis. The pre-processing procedures closely followed the guidelines outlined by Gaser and colleagues (2022), ensuring that the images were prepared according to established standards in the field.

The basic pre-processing steps included realignment, segmentation, spatial normalization, and smoothing of the images. Realignment ensures that the images from each participant are correctly oriented, while segmentation divides the brain into different tissue types, such as GM, WM, and CSF. Spatial normalization involves adjusting the images to fit a standard brain template, allowing for comparisons across participants. Finally, smoothing is applied to the images to enhance signal-to-noise ratios and prepare the data for statistical analysis.

These pre-processing steps are crucial for ensuring that the MRI data is accurately prepared for subsequent analysis, allowing the study to explore the structural differences between the Huffaz and non-Huffaz groups, as well as between male and female participants, with a high degree of precision. The detailed flow of these data preparation procedures is illustrated in the flowchart (Figure 3.2). The process starts from the acquisition of T1-weighted images using a 3T scanner, followed by the transfer of raw DICOM data to a desktop computer. The data then undergoes conversion to NIfTI format, realignment for consistent positioning, segmentation to isolate grey matter, spatial normalization to MNI space using DARTEL, and finally, Gaussian smoothing to enhance data quality for statistical analysis.

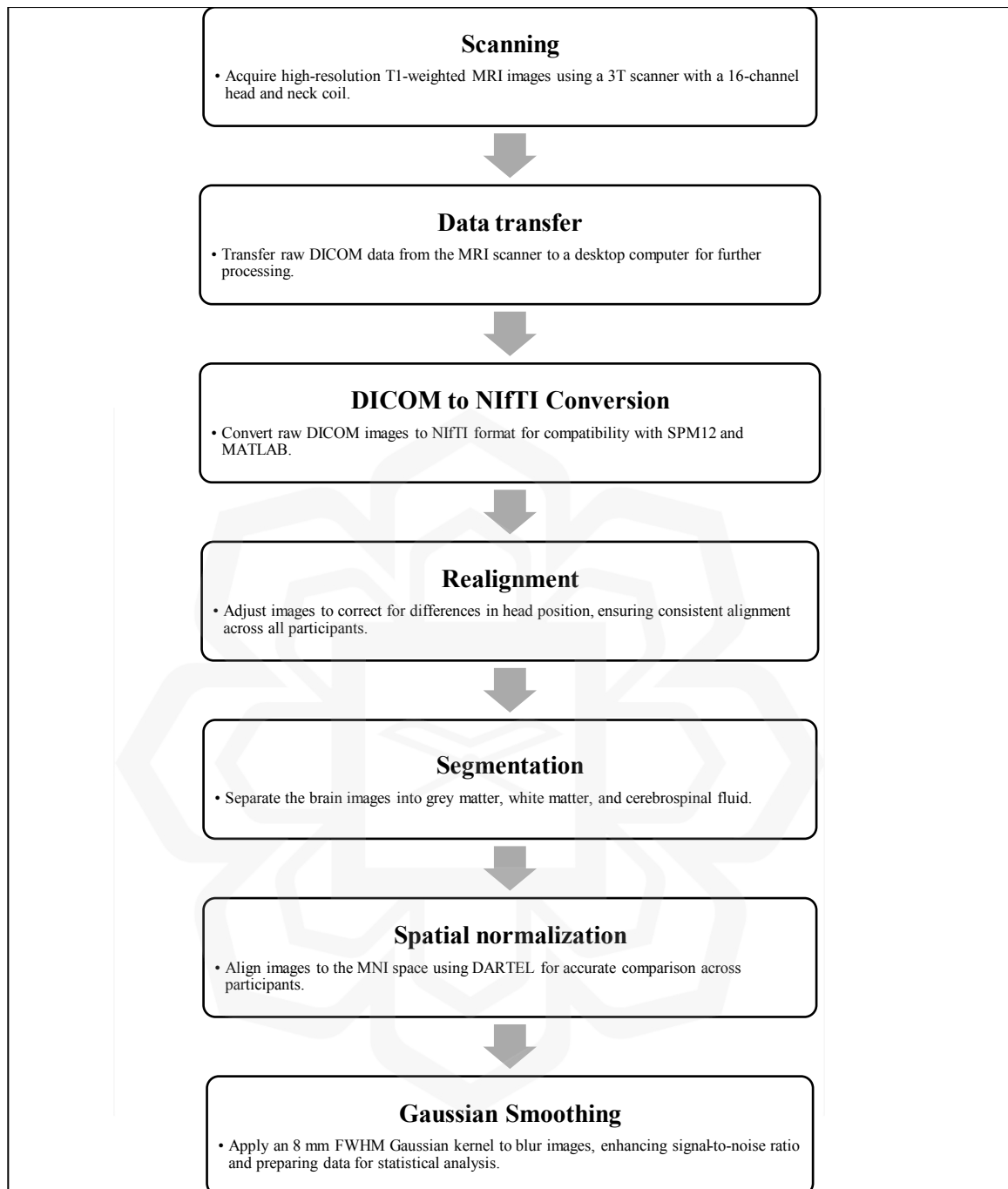


Figure 3.2 Pre-processing Workflow for MRI Data Analysis.

3.5.1 Realignment of MRI Images

Realignment is the critical first step in the pre-processing of MRI images using CAT12. During the image acquisition process, slight differences in head angulation and positioning within the MRI scanner can occur, leading to variations in the positioning of the same anatomical structures across different images. These discrepancies mean that the same brain region may not be aligned in the same coordinate space between scans, potentially compromising the accuracy and comparability of the measurements obtained during analysis.

To address this, the realignment process ensures that the brain orientations across all MRI scans are standardized, allowing for accurate comparisons between images. This step is essential for preventing misregistration of brain anatomical parts, which could lead to significant errors in subsequent analyses and distort the results.

Each MRI image was carefully realigned individually, with the anterior commissure of the brain selected as the reference point for alignment. This reference point was designated as the origin of the matrix coordinate system (0, 0, 0), ensuring consistency across all images. By manually realigning each scan to this coordinate system, the anatomical structures within the brain were consistently positioned, thereby minimizing errors in later data analysis. Figure 3.3 illustrates T1-weighted image from a 21-year-old female Huffaz participant, focusing on the alignment to the anterior commissure. This ensures that the brain's anatomical structures are consistently oriented across all scans, enabling accurate and reliable comparisons in subsequent analyses. Proper realignment is crucial to correct for any variations in head positioning during the MRI acquisition, thereby minimizing potential errors in the interpretation of neuroimaging data.

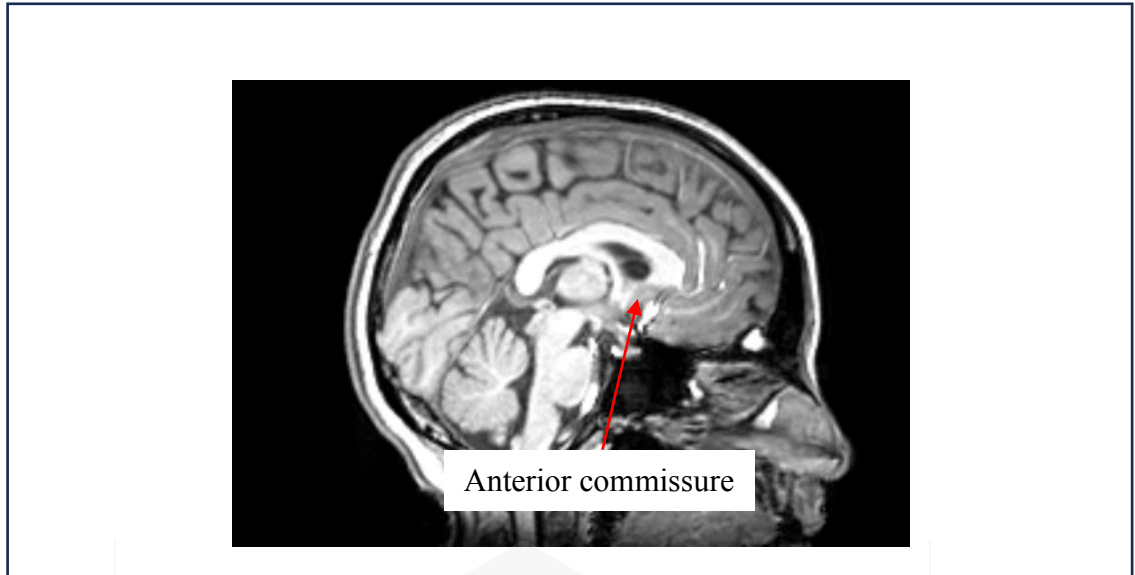


Figure 3.3 Realignment process on sagittal view of a 21-year-old female Huffaz brain highlighting the anterior commissure.

3.5.2 Segmentation of MRI Images

Following the realignment process, the next crucial step in the pre-processing pipeline is segmentation. The segmentation process within the CAT12 toolbox is initiated by applying a spatially adaptive nonlocal means (SANLM) denoising filter, which helps to reduce noise while preserving important structural details in the MRI images. Next step involves partitioning the brain MRI images into distinct tissue types: grey matter, white matter, and cerebrospinal fluid.

The outcome of this segmentation process is the generation of three distinct sets of images derived from the initial T1-weighted MRI scans. This study focuses primarily on grey matter because the T1-weighted MRI protocol employed is particularly effective in highlighting grey matter structures, which are critical for understanding the cognitive processes associated with Quran memorization. T1-weighted images are known for their superior contrast resolution between different tissue types, making them especially well-suited for visualizing grey matter, which contains many neuronal cell bodies and is crucial for various cognitive functions. This focus on grey matter is central to the study's

objectives, as grey matter density and volume are often associated with cognitive abilities, including those potentially influenced by intensive cognitive training such as Quran memorization. Figure 3.4 shows the segmented grey matter (the grey coloured structure) of a 21-year-old female Huffaz participant, derived from T1-weighted MRI images.

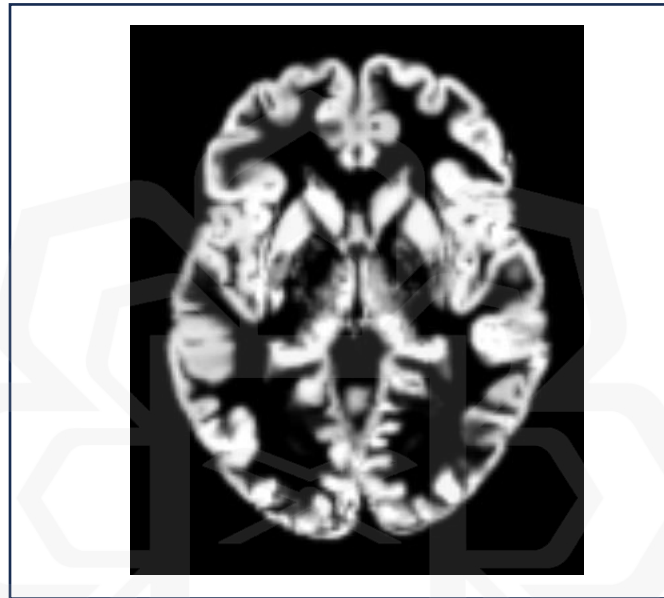


Figure 3.4 Axial view showing the segmentation of grey matter in a 21-year-old female Huffaz brain

3.5.3 Spatial Normalisation of Grey Matter Images

To ensure that the segmented grey matter images were accurately aligned across all participants, spatial normalization was performed to map the images to a standardized space, specifically the Montreal Neurological Institute (MNI) space. The purpose of spatial normalization is to ensure that the anatomical structures in MRI images from one participant correspond spatially to those in other participants, allowing for meaningful comparisons and group analyses.

The CAT12 toolbox enhances the standard preprocessing capabilities of SPM12 by integrating advanced techniques such as Geodesic Shooting (Ashburner & Friston, 2011) and the earlier Diffeomorphic Anatomical Registration Through Exponentiated Lie (DARTEL) method (Ashburner, 2007). The CAT12 toolbox includes pre-existing DARTEL and Geodesic Shooting templates that are already aligned to MNI space, derived from a large sample of 555 healthy control subjects from the IXI-database (Gaser et al., 2022). These templates are available for six different iteration steps, eliminating the need for creating sample-specific templates in most studies.

By using these established templates, the spatial normalization process is both efficient and precise, ensuring that all images are correctly aligned to MNI space. This alignment is critical for accurate group-level analyses and comparisons, particularly in studies examining subtle structural differences such as those related to cognitive training and sexual dimorphism. The integration of these advanced normalization techniques within the CAT12 toolbox allows for a more streamlined and accurate preprocessing pipeline, contributing to the robustness of the study's findings.

3.5.4 Gaussian Smoothing of MRI Images

Following the realignment, spatial normalization, and segmentation processes, the MRI images were subjected to Gaussian smoothing, a critical step in the pre-processing pipeline that prepares the data for statistical analysis. Smoothing involves applying a Gaussian kernel to the images, which effectively blurs them by replacing the intensity of each voxel with a weighted average of the intensities of neighbouring voxels. This process is essential for enhancing the signal-to-noise ratio and increasing the statistical power of the analysis.

For this study, an 8 mm Full Width at Half Maximum (FWHM) Gaussian kernel was applied, which is the default setting in CAT12. This kernel size was chosen to balance the need for smoothing while preserving important anatomical details. The smoothing process helps to reduce noise and variability in the images, making it easier to detect meaningful patterns in the data during subsequent statistical analysis.

While smoothing helps to integrate the data into the Gaussian field model, which is essential for performing valid parametric tests, it also introduces some degree of blurring. This blurring occurs because the smoothing process replaces the intensity of individual voxels with a weighted average, effectively smoothing out fine details. However, smoothing is necessary to reduce between-subject variability and to ensure that the data distribution aligns with the assumptions of Gaussian models, thereby enhancing the validity of statistical comparisons.

Once the smoothing process is complete, the pre-processed data is ready for analysis, allowing the study to investigate the structural differences in brain anatomy related to cognitive training and sexual dimorphism with a high degree of accuracy. Figure 3.5 presents the sagittal view of the smoothed grey matter in the brain of a 21-year-old female Huffaz participant. The image was processed using an 8 mm Full Width at Half Maximum (FWHM) Gaussian kernel to reduce noise and variability, facilitating clearer visualization of brain structures while maintaining crucial anatomical details for further analysis.



Figure 3.5 Sagittal view of smoothed grey matter in a 21-year-old female Huffaz brain

3.6 IMAGE ANALYSIS

The image analysis in this research was systematically designed to achieve the study's aims and objectives through a series of studies examining different aspects of brain structure. The research was divided into three main phases.

The first phase focused on volumetric analysis, comprising two studies: VBM and VOI analysis for volume estimation. The VOI study utilized multiple brain atlases to provide a detailed regional assessment of sex-related differences in brain volume and to evaluate the potential modulating effect of Huffaz training on these differences.

The second phase explored brain complexity, incorporating two distinct approaches: box-counting fractal dimension analysis and Fourier fractal dimension analysis. These studies investigated structural complexity variations in the brain across sexes and examined the influence of cognitive training.

The third phase involved machine learning-based classification, where structural data was used to classify brain sex. In this phase, Huffaz status was included as a feature to assess its impact on model accuracy and determine whether cognitive training influences classification performance.

These analyses were conducted in two stages:

- Initial analysis—without considering Huffaz status.

In the initial analysis, a two-tailed t-test was performed to identify sexual dimorphism in brain structure without accounting for Huffaz status. This test aimed to detect volumetric and complexity differences between male and female participants across the entire brain. Two key comparisons were made; identifying brain regions where males exhibited greater grey matter volume and complexity and detecting regions where females showed greater grey matter volume and complexity.

- Subsequent analysis—with Huffaz status included as a covariate.

To further refine the analysis, Huffaz status was introduced as a covariate in the second phase. This step was crucial for isolating the true impact of sex on brain morphology by accounting for the potential effects of intensive cognitive training associated with Huffaz practices. By controlling for Huffaz status, the analysis ensured that any observed differences in grey matter volume and complexity were primarily attributed to biological sex differences rather than the effects of rigorous memorization training (Sang et al., 2024). Together, these comprehensive analyses provided a robust understanding of sex-related differences in brain structure while considering the potential impact of cognitive training.

3.6.1 Volumetry Analysis

The volumetric analysis in this Ph.D. research involved two complementary studies: VBM and VOI volume estimation (Giuliani et al., 2005; Seyedi et al., 2020; Snook et al., 2007). Both methods were employed to investigate sexual dimorphism in brain structure, each offering unique insights into how male and female brains differ in terms of grey matter volume, as well as how cognitive training (Huffaz status) modulates these differences.

VBM is a whole-brain, unbiased approach that examines grey matter volume differences across the entire brain at the voxel level (Ashburner & Friston, 2000). By applying statistical tests voxel by voxel, VBM identifies areas of the brain where significant differences exist between groups (in this case, between males and females). The advantage of VBM is that it provides a global overview of brain structure, allowing for the identification of any region that shows sex-related differences without requiring a priori knowledge or selection of specific regions. This whole-brain approach is particularly useful for detecting unexpected or widespread patterns of sexual dimorphism in brain volume. However, while VBM offers a comprehensive and unbiased analysis, it may lack the specificity and sensitivity needed to detect smaller, localized differences in brain structure, especially in regions that are not well-captured by global statistical approaches.

In contrast, VOI analysis focuses on specific brain regions, providing a more detailed examination of grey matter volume within predefined areas of interest. This method relies on probabilistic brain atlases, such as the Neuromorphometrics, CoBrA, LPBA40, and SUIT atlases, to segment and define brain regions for analysis. By estimating the volume of specific regions rather than analysing the entire brain voxel by voxel, VOI analysis can provide a more targeted assessment of regional differences between groups.

The use of multiple brain atlases in this study further refined the analysis, enabling a more accurate investigation of cortical and subcortical structures, including areas like the cerebellum and brainstem, which are often overlooked in whole-brain VBM studies (van Eijk et al., 2020). This regional focus allowed for the identification of sexual dimorphism in specific areas, providing a complementary analysis to the global approach of VBM.

Additionally, the VOI approach was enhanced by analysing the effects of Huffaz training, allowing for the exploration of how cognitive training influenced specific brain regions.

The decision to conduct both VBM and VOI volume estimation studies was based on their complementary strengths. VBM provided a broad, unbiased view of sexual dimorphism across the entire brain, enabling the identification of large-scale patterns and unexpected differences between males and females. Meanwhile, VOI analysis offered a more detailed, region-specific examination of brain structures, particularly in subcortical areas such as the cerebellum, that may not be fully captured by VBM alone.

By employing both methods, the research was able to capitalize on the strengths of each approach. VBM allowed for a global assessment of sexual dimorphism, while VOI focused on more detailed and anatomically defined brain regions, enabling a deeper investigation of the effects of sex and cognitive training on specific brain structures. This dual approach provided a robust and comprehensive analysis, ensuring that the study captured both broad patterns and localized differences in brain volume between males and females, with and without considering the influence of Huffaz cognitive training.

3.6.1.1 Study 1: Voxel-Based Morphometry Analysis

For the analysis of sexual dimorphism in brain structure, the SPM-CAT12 toolbox was employed within the framework of the General Linear Model (GLM). The VBM analysis was designed to explore differences in grey matter morphology between males and females, both with and without accounting for the influence of intensive cognitive training (Huffaz status).

To control for multiple comparisons across the entire brain, Family-Wise Error (FWE) correction was applied with a significance level set at $p < 0.05$. FWE correction is a stringent statistical method used to reduce the risk of Type I errors (false positives), ensuring that any significant results are robust and not due to chance. The analysis also

employed an extent threshold of 100 voxels, meaning that only clusters of this size or larger were considered significant. This threshold was implemented to ensure that the detected differences were both statistically and anatomically meaningful, filtering out smaller, potentially noise-driven clusters.

The analyses were also corrected for total intracranial volume (TIV) by default within the CAT12 framework. Correcting for TIV is recommended in neuroimaging studies to ensure that the analysis focuses on relative differences in brain structure, independent of overall brain volume. This step refines the results by accounting for individual differences in brain size, ensuring that the findings reflect true anatomical variations related to sex (Del Mauro et al., 2022).

3.6.1.2 Study 2: Voxel of Interest Analysis

In the second phase of the 3D volumetry analysis, regional grey matter (GM) tissue volumes were estimated using the CAT12 toolbox, based on several well-established brain probabilistic atlases. The atlases included in this analysis were the Neuromorphometrics atlas, the Computational Brain Anatomy Laboratory (CoBrA) atlas, the Laboratory of Neuro Imaging (LONI) Probabilistic Brain Atlas (LPBA40), and the Spatially Unbiased Atlas Template of the Cerebellum and Brainstem (SUIT) atlas (Diedrichsen, 2006). Notably, both the CoBrA and SUIT atlases are specifically designed for subcortical structures, providing detailed regional information about areas such as the cerebellum and brainstem, which are essential for understanding sex-related differences in subcortical morphology.

Additionally, a customized MATLAB script was used to estimate regional grey matter volumes based on the Talairach Daemon (TD) probabilistic atlas (Lancaster et al., 2000). By extracting data from these probabilistic atlases, grey matter volumes were calculated for various brain structures, both cortical and subcortical. These volumes served as the foundation for subsequent statistical analyses to explore differences between males and females.

After performing the normality checks to confirm the appropriateness of the data for parametric analysis, an initial analysis was conducted using two-tailed t-tests without considering the Huffaz group. This initial analysis aimed to identify baseline sex differences in brain volume across the entire sample before accounting for the potential effects of cognitive training. These t-tests were conducted to determine whether significant differences existed in grey matter volume between males and females in the various brain regions derived from the atlases.

Following this initial t-test analysis, the primary analysis was conducted using an analysis of covariance (ANCOVA) to compare grey matter volumes between males and females, while controlling for the potential confounding effects of Huffaz versus Non-Huffaz status. This method allowed for an assessment of sex differences in brain morphology while accounting for the possible impact of intensive memorization practices associated with the Huffaz training.

A significance level of 0.05 was chosen for comparisons between the two groups (males and females), ensuring a rigorous statistical threshold to minimize false positives. All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS, version 29.0; IBM-SPSS, Chicago, IL). The ANCOVA model enabled the identification of regions exhibiting sexual dimorphism, while correcting for the effects of cognitive training and total brain volume. By using both cortical and subcortical atlases, the analysis provided a detailed view of how sexual dimorphism manifests across various brain regions, ensuring that observed differences were robust and not influenced by the participants' cognitive training or overall brain size.

3.6.2 Complexity Index Analysis

In addition to volumetric analysis, this research also employed complexity measures to further explore the structural differences between male and female brains. While volumetric analysis focuses on assessing the size and volume of brain structures in three-

dimensional (3D) space, it does not provide information about the geometric complexity or structural irregularities within these regions. To address this, complexity measures such as FD analysis were introduced to capture the intricacy and self-similarity of brain structures that are often overlooked in standard volumetric assessments.

FD measures offer a complementary approach to volumetric analysis by quantifying the complexity of an object or structure. In the context of neuroimaging, these methods evaluate how the surface or structure of the brain becomes more intricate or irregular as spatial resolution increases. This additional dimension of analysis provides insights into the internal organization of the brain, revealing structural differences that may not be apparent when only measuring volume.

Volumetric analysis, as conducted in the VBM and VOI studies, examines the size and shape of different brain regions, focusing on the absolute or relative volumes of grey matter. This approach is critical for identifying differences in brain size between males and females. However, volume alone does not account for how complex the structure of a region might be, or how the tissue is distributed across the 3D space.

In contrast, complexity measures such as FD offer a more nuanced understanding of brain structure by assessing the level of detail or irregularity within the geometry of the brain. While volumetric analysis can indicate that one brain region is larger or smaller than another, FD analysis reveals whether that region's structure is more complex, with greater variability and self-similar patterns, or whether it is more uniform. For this thesis, two FD methods were employed:

3.6.2.1 Study 3: Box-Counting Fractal Dimension Analysis

The box-counting method is a commonly used technique for estimating the FD of an object by covering it with a grid of boxes and counting how many boxes contain part of the object. This process is repeated at different scales, and the FD is calculated based on how the number of occupied boxes changes with scale. In neuroimaging, this method provides a

measure of how complex the surface or structure of a brain region is across different spatial resolutions, revealing intricate differences in the geometry of male and female brains.

3.6.2.2 Study 4: Fourier Fractal Dimension Analysis

The Fourier method is another approach to estimating FD, relying on frequency-based transformations to analyse the patterns in the brain's structure. This method transforms the brain image data into a frequency domain using Fourier analysis, allowing for a calculation of how complexity varies across different frequency components. The Fourier fractal dimension provides an additional perspective on brain complexity, particularly useful for capturing more subtle or diffuse structural variations that may not be detected by box-counting.

The introduction of complexity measures alongside volumetric analysis is essential for capturing the full range of structural differences between male and female brains. While volumetric analysis reveals the size of brain regions, FD analysis provides critical insights into how those regions are organized and how complex their structures are. By employing both box-counting and Fourier FD analyses, this research offers a comprehensive examination of brain complexity, allowing for a deeper understanding of the underlying geometric patterns that differentiate male and female brain structures. These complexity measures also enable the exploration of how cognitive training, such as Huffaz memorization, influences the organization of the brain, providing a more complete picture of how brain structure is shaped by both biological sex and cognitive activity.

Steps in Fractal Dimension Analysis

1) Defining Brain Regions of Interest:

Brain regions of interest were defined using the TD probabilistic atlas (Lancaster et al., 2000), which provided a consistent framework for extracting cortical and subcortical brain regions across all participants. These regions were then subjected to FD analysis using both the box-counting and Fourier transform methods.

2) Fractal Dimension Calculation:

The two FD methods were used to compute the complexity of brain structures. These methods were applied using two custom MATLAB scripts to precisely compute the complexity of brain structures, providing a detailed assessment of the geometric patterns and organizational complexity of male and female brains.

3) Statistical Analysis:

First, normality checks were performed to ensure that the data met the assumptions for parametric testing. Following this, a preliminary t-test was conducted to explore the effect of sex on brain complexity without considering Huffaz group status. This initial t-test provided a baseline understanding of sex-related differences in complexity prior to adjusting for the influence of intensive cognitive training.

After the t-test, the primary analysis was conducted using analysis of covariance (ANCOVA). This allowed for the examination of the effect of sex on grey matter complexity, while controlling for Huffaz status (memorization expertise). The inclusion of

Huffaz status as a covariate ensured that any observed differences in brain complexity were due to sex, independent of the cognitive training associated with Quran memorization.

Similar to the volumetric analysis, the FD analysis was conducted in two directions:

- a) Male > Female: To identify regions where males exhibited higher complexity than females.
- b) Female > Male: To identify regions where females exhibited higher complexity than males.

A higher FD indicates greater structural complexity, meaning that the brain region displays more intricate, irregular patterns. Increased complexity may reflect a more elaborate neural architecture, potentially associated with specialized cognitive or functional capacities. Finding higher complexity in specific regions for males or females can suggest sex-specific neural adaptations.

Conducting the analysis in two directions —Male > Female and Female > Male— allowed for the detection of regions where one sex exhibited more intricate brain structures than the other. This dual-direction analysis, along with FD measures, deepened the understanding of how brain complexity varies between sexes and how these differences might be influenced by cognitive training like Huffaz memorization. By using both volumetric and complexity analyses, the study captured a fuller picture of the structural variations between males and females, including not just size differences but also the underlying organizational complexity.

The statistical significance threshold was set at $p < 0.05$, ensuring that results reflected true differences between the sexes. All statistical analyses were performed using SPSS (version 29.0; IBM-SPSS, Chicago, IL), providing a robust framework for examining the relationship between sex, cognitive training, and brain complexity.

3.6.3 Brain Sex Classification

In recent years, ML has gained prominence in neuroimaging due to its ability to handle complex, high-dimensional data more effectively than traditional statistical methods. Classical statistical techniques, such as those utilised in Study 1-4, are typically well-suited for datasets where predefined hypotheses are tested against a limited number of variables. These traditional methods rely heavily on assumptions about the data's distribution and linearity, and they often struggle when the relationships between variables are non-linear or involve high levels of interaction.

In contrast, ML excels in detecting patterns within large datasets, even when those patterns are subtle or non-linear. Unlike classical statistics, ML does not require explicit assumptions about the data's underlying distribution, making it more flexible and scalable for complex data, such as neuroimaging datasets. ML algorithms can also learn from the data itself, automatically identifying relevant features and relationships that might be missed by classical techniques. This makes ML particularly valuable in tasks like brain sex classification, where the structural differences between male and female brains may be subtle and distributed across many regions. Moreover, ML methods can handle interactions between features in ways that classical approaches cannot easily manage, leading to more accurate and insightful predictions.

3.6.3.1 Study 5: Machine Learning-Based Brain Sex Classification

As the complexity of neuroimaging data continues to grow, ML has become indispensable for uncovering nuanced differences in brain morphology and function, making it a powerful complement to traditional statistical approaches.

In this study, four ML algorithms were selected—logistic regression, support vector machine, deep learning, and random forest—based on a systematic review conducted in

Chapter 2. The review highlighted the efficacy of these algorithms in neuroimaging research, particularly for classification tasks involving high-dimensional brain data. Below is a brief explanation of each algorithm used in this study:

- Logistic Regression:

Logistic regression is a widely used algorithm for binary classification tasks. It estimates the probability that a given input belongs to one of two categories, based on a linear decision boundary. Despite being simple, logistic regression is highly effective for tasks where the relationship between the features and the outcome is approximately linear, making it a useful baseline in ML analyses.

- Support Vector Machine:

SVM is a powerful algorithm that aims to find the hyperplane that best separates the data into two classes. By maximizing the margin between the two categories (male and female, in this case), SVM creates a robust decision boundary. When data is not linearly separable, kernel functions can be applied to transform the data into higher dimensions for better classification performance. SVM is particularly effective in handling small datasets and complex boundaries.

- Deep Learning:

Deep learning is a subset of ML that uses artificial neural networks to learn patterns from data. In this study, a deep learning model with two hidden layers was employed to capture non-linear relationships in the data. Deep learning models are particularly suited to complex tasks like brain classification because they can automatically learn high-level features and provide strong performance even with large datasets.

- Random Forest:

Random forest is an ensemble method that builds multiple decision trees during training and aggregates their predictions to improve accuracy. By randomly selecting subsets of data and features for each tree, the algorithm reduces the risk of overfitting and increases model robustness. Random forest is well-suited for non-linear data and provides a reliable classification approach, especially in cases where individual decision trees may be too simplistic.

These algorithms, chosen for their robustness and ability to handle both linear and non-linear relationships, were implemented to classify brain sex based on the structural features derived from volume and FD analyses. Through their application, this study aimed to uncover how these features vary between males and females, with and without consideration of cognitive training.

The final study of this research applied ML techniques to classify brain sex using features derived from Study 2 through Study 4 above. These features, which included both volumetric and FD measures, were analysed to evaluate their effectiveness in differentiating between male and female brain structures. Additionally, the role of Huffaz status in influencing classification performance was examined to assess how intensive cognitive training impacts brain structure and sex prediction.

The features used for the ML analysis were extracted from the volume (Study 2) and FD analyses (Study 3 and 4) conducted in Study 2 through Study 4. By combining both volumetric and complexity measures, the ML models aimed to capture detailed structural characteristics of male and female brains, ensuring a comprehensive dataset for classification tasks. The inclusion of both complexity and volume-based features allowed the models to assess sex-based differences in brain morphology with a greater degree of accuracy.

Four ML algorithms were selected for the analysis, based on prior systematic review (Chapter 2) and their availability in AI Studio (version 2024.0.1). The algorithms included logistic regression, support vector machine, deep learning and random forest. The deep learning employed in the AI Studio software is based on a multi-layer feed-forward artificial neural network trained using stochastic gradient descent with back-propagation. Each algorithm was implemented using the default settings in AI Studio, with the dataset split into 70% training and 30% testing sets to ensure robust model development (Nguyen et al., 2021). The Huffaz/non-Huffaz status was included as a predictor variable to examine how cognitive training influenced the classification performance of these models.

The performance of each ML algorithm was evaluated using several key metrics:

- Accuracy: The proportion of correctly classified instances.
- Area Under the Curve (AUC): A measure of the model's ability to differentiate between male and female participants.
- Sensitivity: The true positive rate, reflecting the model's ability to correctly classify male participants.
- Specificity: The true negative rate, indicating the model's ability to correctly classify female participants.

By comparing the performance of these four algorithms, the study aimed to identify the most effective model for predicting brain sex. Additionally, a combination of these models' predictions was explored to enhance robustness and generalizability, reducing the likelihood of model bias.

Each ML algorithm was fine-tuned with specific hyperparameters to optimize model performance as in the Table 3.2. These hyperparameter settings were selected based on default configurations, balancing model complexity with generalizability. The objective was to minimize overfitting while maximizing predictive performance, ensuring that the models could generalize effectively to unseen data.



Table 3.2 Summary of hyperparameters for the four machine learning algorithms used in the study.

Algorithm	Hyperparameters
Logistic Regression	- Solver: Automatic - Stopping Criteria: 3 rounds or tolerance of 0.001 - Data Standardization: Enabled - Early stopping: Enabled
Support Vector Machine	- Kernel type: Dot - Complexity Constant (C): 0 - Convergence Epsilon: 0.001 - Positive Loss Function: 1.0 - Negative Loss Function: 1.0 - Epsilon Parameters: 0 (epsilon, epsilon plus, epsilon minus)
Deep Learning	- Activation Function: Rectifier - Hidden Layer sizes: 50:50 - Training Epochs: 10
Random Forest	- Number of Trees: 100 - Criterion: Gain Ratio - Guess subset ratio: Enabled - Voting strategy: Confidence Vote

CHAPTER FOUR

RESULTS

4.1 INTRODUCTION

This chapter presents the findings from the analyses conducted in the previous chapter, encompassing all aspects of the investigation into brain sexual dimorphism and the potential modulating effects of cognitive training, specifically Huffaz practices. The results are organized around the core objectives of the study, addressing both volumetric and complexity measures, as well as machine learning-based classification techniques.

The findings begin with the VBM analysis, highlighting the differences in grey matter volume between males and females, both before and after controlling for Huffaz status. This is followed by the VOI analysis, where regional brain volumes were estimated using multiple brain atlases to further explore sex-related differences in specific regions. The chapter also includes results from the FD analyses, using both box-counting and Fourier methods, to examine the complexity of brain structures and their association with sex and cognitive training. Lastly, the chapter presents the outcomes of the ML analysis, where classification algorithms were applied to predict brain sex based on volumetric and complexity features derived from previous studies.

Together, these findings provide a comprehensive view of how sex and cognitive training influence brain structure, contributing novel insights to the fields of neuroimaging and cognitive neuroscience.

4.2 STUDY 1: VOXEL BASED MORPHOMETRY ANALYSIS

The first section of the results chapter presents the findings from the VBM analysis conducted to investigate sexual dimorphism in brain structure. The results are organized to first highlight the general differences in grey matter volume between males and females, followed by a detailed examination of how these differences are influenced by cognitive training, specifically the rigorous memorization practices of the Huffaz group. The analysis was performed in two directions: identifying brain regions where males exhibit larger grey matter volumes than females, and vice versa. Additionally, the impact of Huffaz status as a covariate was considered to isolate the effects of sex on brain morphology. The results presented in this section provide critical insights into the structural underpinnings of sexual dimorphism in the brain and the potential modulating effects of cognitive training.

The VBM analysis revealed that males exhibited larger volumes in several brain regions compared to females including the cerebellum, temporal gyrus, fusiform gyrus, parahippocampal gyrus, and hippocampus. Notably, when controlling for Huffaz status—reflecting individuals who have undergone intensive Quran memorization—additional sex-related volumetric differences emerged in the hypothalamus, amygdala, lingual gyrus, and cingulate cortex, highlighting the nuanced impact of cognitive training on brain structure. Interestingly, no regions were consistently found where females had significantly larger volumes than males. This pattern of findings underscores the presence of sex-specific structural differences in the brain, particularly favouring males in terms of grey matter volume.

The specific brain regions identified, along with their MNI coordinates (X, Y, Z) of the peak voxels showing significant alterations in the male > female contrast, are detailed in Table 4.1 and

Table 4.2. These tables highlight the regions where significant differences were observed, with corrections applied using the family-wise error (FWE) method, maintaining a p-value threshold of < 0.05 . These findings provide robust evidence of sexual dimorphism in brain structure, particularly in regions where males demonstrate larger grey matter volumes and offer insights into how these differences may be influenced or independent of cognitive training practices such as those undertaken by the Huffaz group.

Table 4.1 Brain regions of significant sexual difference between males and females before controlling for Huffaz group.

Region (Male>female)	Cluster Size (Voxel counts)	Z statistic	x	y	z
Primary visual cortex, cerebellar tonsil, right cerebellar tonsil	1438	6.63	-2	-90	-12
		6.31	-9	-90	-21
		5.87	9	-86	-14
Left cerebellum, left cerebellar tonsil, left cerebellar lobule VIIb/VIII	1761	6.53	-18	-64	-28
		5.69	-21	-66	-36
		5.27	-15	-76	-30
Right cerebellar lobule VIIB/VIII, right cerebellar lobule VIIB/VIII, right cerebellar lobule VI	3712	6.42	26	-56	-32
		6.28	20	-62	-30
		5.65	30	-45	-20
Left parahippocampal gyrus, left anterior parahippocampal gyrus, left fusiform gyrus	2150	6.27	-18	-6	-30
		6.10	-30	0	-24
		5.84	-28	-14	-10
Left middle temporal gyrus, left parahippocampal gyrus	263	6.11	-44	8	-48
		5.19	-36	2	-45

Right parahippocampal gyrus, right fusiform gyrus, right parahippocampal gyrus	3628	6.10	16	2	-21
		5.98	28	-14	-9
		5.97	16	-3	-28
Left orbitofrontal cortex	358	5.87	-33	38	-21
Left inferior temporal gyrus, left middle temporal gyrus	233	5.54	-40	-56	-20
		5.39	-51	-69	-22
Medial prefrontal cortex	195	5.48	0	24	-8
Posterior cingulate cortex	142	5.47	3	-42	8
Left cerebellar lobule VIIB/VIII	176	5.44	-20	-45	-26

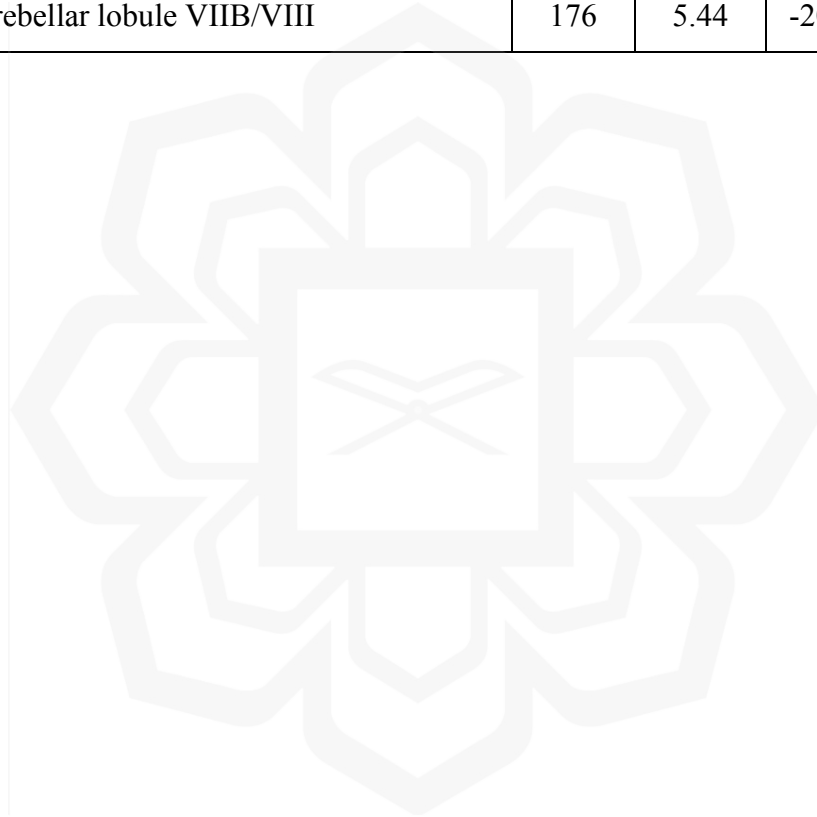


Table 4.2 Brain regions of significant sexual difference between males and females after controlling for Huffaz group.

Region (Male>female)	Cluster Size (Voxel counts)	Z statistic	x	y	z
Left cerebellar lobule VIIb/VIII, primary visual cortex, right lingual gyrus	7048	7.49	-16	-66	-27
		6.66	2	-93	-15
		6.47	9	-84	-14
Right cerebellar lobule VIIb/VIII, right cerebellar lobule VIIb/VIII, right inferior temporal gyrus	7398	7.40	27	-56	-30
		7.26	20	-62	-30
		6.82	30	-48	-21
Hypothalamus, right amygdala, right parahippocampal gyrus	12522	7.01	-3	12	-18
		6.98	15	3	-18
		6.93	27	-10	-14
Posterior cingulate cortex, posterior cingulate cortex	818	6.43	0	-46	18
		5.73	4	-42	9
Left parahippocampal gyrus, left parahippocampal gyrus	358	6.16	-42	9	-48
		5.40	-36	3	-45

4.3 STUDY 2: VOXEL OF INTEREST ANALYSIS

The second section of the results chapter presents the findings from the VOI analysis, focusing on the estimation of regional brain volumes across multiple probabilistic brain atlases. Unlike the VBM approach, which provides a whole-brain analysis, VOI specifically targets predefined brain regions to assess volumetric differences between males and females. This analysis utilized various brain atlases, including the Neuromorphometrics, CoBrA, LPBA40, and SUIT atlases, to ensure comprehensive coverage of both cortical and subcortical structures.

In this section, the results will reveal regional volumetric differences between males and females, both before and after controlling for Huffaz status. By focusing on specific regions of interest, the VOI analysis allows for a more detailed exploration of sexual dimorphism in brain structure, offering insights into how these differences manifest in distinct anatomical areas.

Similar to the VBM analysis, the VOI analysis examined volumetric differences in both directions: regions where males exhibited significantly larger volumes than females, and regions where females showed larger volumes than males. This two-directional approach ensures a comprehensive understanding of the brain volume differences between the sexes and explores whether these differences are influenced by cognitive training, such as the memorization practices of Huffaz.

The VOI analysis showed consistent results with the VBM analysis across all brain atlases, indicating that male brains consistently exhibited greater volume in the examined regions compared to females. No regions were found to be larger in females than in males.

Table 4.3 presents the significant brain regions ($p < 0.05$) where male volumes were larger than female volumes. The analysis shows that the male > female differences in brain volume are widespread across various cortical and subcortical regions. Even after

controlling for Huffaz status, only a few additional regions reached statistical significance (marked with * in the table).

Within the cortical areas, significant volumetric differences are observed in the frontal, parietal, temporal, and occipital cortices. However, regions that do not fall within these four main lobes or are situated at the intersections between these lobes are categorized as other regions. These areas, which include structures such as the insula, cingulate gyrus, and subcallosal cortex, play important roles in the connectivity and integration of brain functions across different cortical areas. The presence of male-dominant volumetric differences in these "other regions" further underscores the extensive and complex nature of sexual dimorphism in brain structure.

In

Table 4.3, the right column details the male > female volumetric differences found in subcortical structures. While all five atlases contain information on subcortical regions, the SUI and CoBrA atlases specifically focus on these structures, providing more detailed parcellation compared to the other atlases. These two atlases offer greater granularity, especially in areas like the cerebellum, which is divided into multiple subregions, such as the vermis I to X (in Roman numerals), providing a more refined analysis of subcortical volumetric differences. This allows for a more comprehensive understanding of sexual dimorphism in the subcortical areas, emphasizing that the differences are not just general but can be found in very specific subdivisions of key brain regions. All reported volumes indicate larger mean in males compared to females with significant level, $p < 0.05$. After controlling for Huffaz group, regions are marked with *.

Additionally, Table 4.4 and Figure 4.1 provides the average absolute brain volume differences between males and females, categorized according to the different brain probabilistic atlases used in the analysis. The bar chart (Figure 4.1) compares the percentage differences in brain volume, where male brain volumes are larger than female brain volumes. The SUI atlas shows the highest volume difference (12.41%), followed by CoBrA (11.88%), Neuromorphometric (10.42%), LPBA40 (9.95%), and TD (5.74%). This

detailed comparison offers further insight into the regions of the brain where sexual dimorphism in volume is most pronounced.

Table 4.3 Voxel-of-interest analysis using 5 probabilistic brain atlases.

Probabilistic brain atlases	Cortical structures	Subcortical structures
All atlases	<u>Frontal cortex:</u> superior frontal gyrus, inferior frontal gyrus, middle frontal gyrus, precentral gyrus, gyrus rectus <u>Parietal cortex:</u> precuneus, left supramarginal gyrus, angular gyrus <u>Temporal cortex:</u> superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, parahippocampal gyrus <u>Occipital cortex:</u> superior occipital gyrus, middle occipital gyrus, inferior occipital gyrus, cuneus, lingual gyrus	cerebellum, hippocampus, putamen, caudate

	<u>Other regions:</u> fusiform gyrus, cingulate gyrus, insula	
Neuromorphometric	<u>Frontal cortex:</u> Both sides: frontal operculum, supplementary motor cortex, superior frontal gyrus, triangular part of the inferior frontal gyrus, frontal pole, middle frontal gyrus, precentral gyrus, medial orbital gyrus, lateral orbital gyrus, anterior orbital gyrus, posterior orbital gyrus, gyrus rectus right precentral gyrus medial segment, left superior frontal gyrus medial segment, right opercular part of the inferior frontal gyrus, left orbital part of the inferior frontal gyrus, <u>Parietal cortex:</u> Both sides: precuneus, superior parietal lobule, angular gyrus left parietal operculum, right postcentral gyrus medial	Both sides: amygdala, hippocampus, cerebellum exterior, accumbens area, bilateral caudate, pallidum (globus pallidus), putamen, basal forebrain cerebellar vermal lobules I-V, cerebellar vermal lobules VI-VII, cerebellar vermal lobules VIII-X,

	segment, left supramarginal gyrus <u>Temporal cortex:</u> Both sides: superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, temporal pole, entorhinal area, parahippocampal gyrus, planum polare <u>Occipital cortex:</u> Both sides: occipital pole, occipital fusiform gyrus, superior occipital gyrus, middle occipital gyrus, inferior occipital gyrus, cuneus, lingual gyrus <u>Other regions:</u> Both sides: fusiform gyrus, anterior cingulate gyrus, posterior cingulate gyrus, anterior insula, posterior insula, subcallosal area	
LPBA40	<u>Frontal cortex:</u> Both sides: superior, middle and inferior frontal gyrus,	Both sides: putamen, hippocampus, caudate, cerebellar lobe

	precentral gyrus, middle orbitofrontal gyrus, gyrus rectus, *Lateral orbitofrontal gyrus <u>Parietal cortex:</u> Both sides: superior parietal gyrus, precuneus, angular gyrus *Postcentral gyrus left supramarginal gyrus <u>Temporal cortex:</u> Both sides: superior, middle and inferior temporal gyrus, parahippocampal gyrus <u>Occipital cortex:</u> Both sides: superior, middle and inferior occipital gyrus, lingual gyrus, cuneus <u>Other regions:</u> Both sides: fusiform gyrus, insula, cingulate gyrus	
TD	Whole cerebrum, frontal lobe, occipital lobe, parietal lobe, temporal lobe <u>Frontal cortex:</u> superior, middle and inferior frontal gyrus, gyrus rectus	<u>Cerebellum:</u> cerebellum anterior lobe, cerebellum posterior lobe, cerebellar lingual, cerebellar tonsil, culmen, culmen of

	*Medial frontal gyrus, orbital gyrus, precentral gyrus <u>Parietal cortex:</u> Superior and inferior parietal lobule, precuneus, supramarginal gyrus, angular gyrus <u>Temporal cortex:</u> superior, middle and inferior temporal gyrus, parahippocampal gyrus <u>Occipital cortex:</u> superior, middle and inferior occipital gyrus, cuneus, lingual gyrus <u>Other regions:</u> anterior cingulate, posterior cingulate, cingulate gyrus, fusiform gyrus, insula, paracentral lobule, subcallosal gyrus,	vermis, declive, declive of vermis, inferior semilunar lobule, lentiform nucleus, pyramis, pyramis of vermis, tuber, tuber of vermis, uvula amygdala, hypothalamus, limbic lobe, caudate body, head and tail, lateral and medial globus pallidus, subthalamic nucleus, dentate, hippocampus, lateral geniculum body, putamen, claustrum
SUIT		<u>Cerebellum:</u> Both sides: I IV, V, VI, Crus I, Crus II, VIIb, VIIla, VIIlb,

		Vermis VI, Vermis Crus II, Vermis VIIb, Vermis VIIa, Vermis VIIb, Vermis IX and Vermis X
CoBrA		<u>Cerebellum:</u> Both sides: anterior cerebellar lobule I-II, anterior cerebellar lobule III, anterior cerebellar lobule IV, anterior cerebellar lobule V, superior posterior cerebellar lobule VI, superior posterior cerebellar lobule crus I, superior posterior cerebellar lobule crus II, superior posterior cerebellar lobule VIIb, inferior posterior cerebellar lobule VIIa, inferior posterior cerebellar lobule VIIb, inferior posterior cerebellar lobule X right inferior posterior cerebellar lobule IX <u>Other regions</u> Both sides: amygdala, hippocampus CA1, striatum, globus pallidus, Subiculum,

		CA4/Dentate Gyrus, and Stratum Radiatum/ Lacunosum/ Moleculare Left CA2/CA3
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Table 4.4 Average absolute brain volume difference of male>female based on probabilistic atlas.

Probabilistic brain atlas	Volume difference (%)
Neuromorphometric	10.42%
LPBA40	9.95%
TD	9.74%
SUIT	12.41%
CoBrA	11.66%

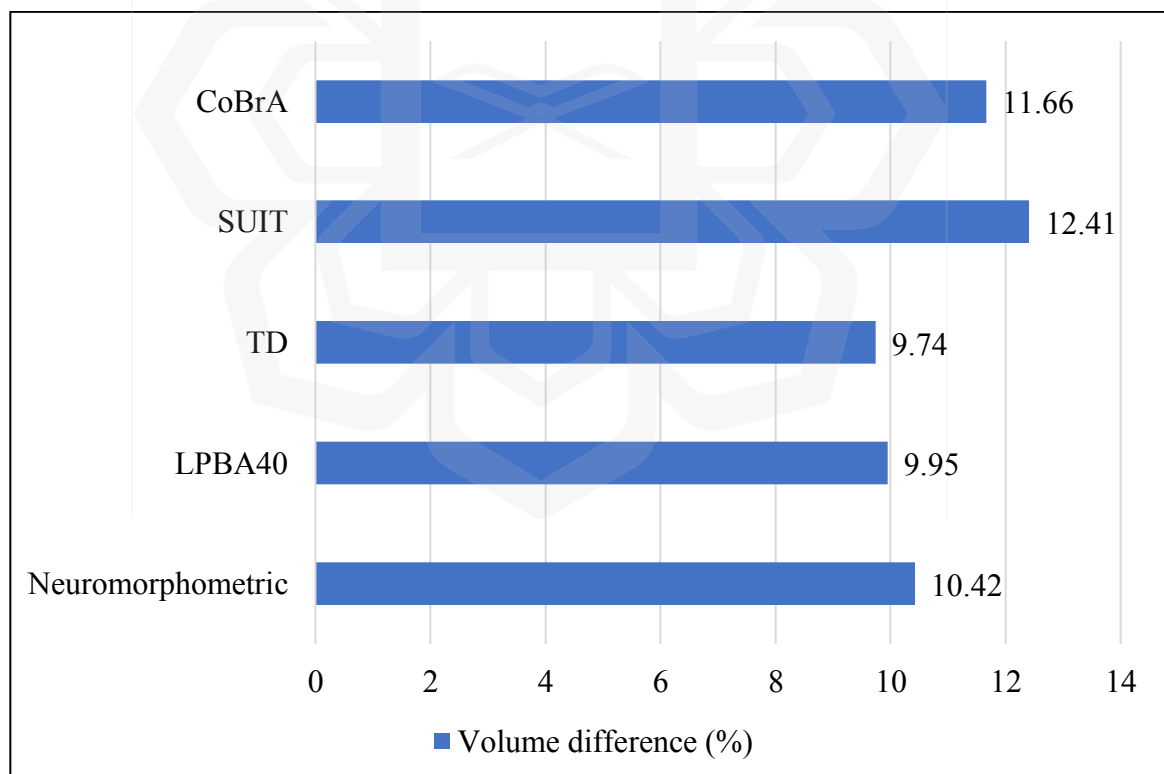


Figure 4.1 Average Absolute Brain Volume Difference (%) Between Males and Females Across Different Probabilistic Atlases.

4.4 STUDY 3: BOX-COUNTING FRACTAL DIMENSION ANALYSIS

This section of the results chapter presents the findings from the box-counting fractal dimension (BCFD) analysis, which was used to assess the complexity of brain structures in relation to sexual dimorphism. Unlike volumetric analysis, which focuses on the size and volume of brain regions, FD analysis provides a measure of how intricate and detailed the structure of the brain is. The box-counting method specifically estimates complexity by examining how well a structure fills space across multiple scales, offering a quantitative assessment of geometric irregularities and self-similar patterns within brain regions.

By applying this method, the study aimed to explore whether males and females differ in terms of brain complexity, both in cortical and subcortical structures. The analysis was conducted in two directions: identifying regions where males have higher complexity than females, and regions where females demonstrate higher complexity than males. This approach provides a deeper understanding of sexual dimorphism by revealing not only size differences but also differences in the intricate architecture of the brain's surface and internal structures.

The BCFD analysis identified significant sex-related differences in brain complexity across several regions. Even after controlling for Huffaz status, many of these differences persisted, suggesting that the observed sexual dimorphism in brain complexity is inherent rather than significantly influenced by the cognitive training associated with Quran memorization. Notably, regions such as the declive and lingual gyrus continued to show significant sex differences, indicating robust patterns of structural complexity between males and females. The following tables, Table 4.5 and 4.6, provide a detailed summary of these key findings. The brain regions were analysed for sex differences in fractal dimension (FD), and those showing significant differences were categorized as either male-dominant (higher FD in males) or female-dominant (higher FD in females).

Table 4.5 Box-counting FD-Uncontrolled for Huffaz.

Brain region	Female		Male		P-value
	Mean FD	SD	Mean FD	SD	
Male>female					
Clastrum	1.192	0.011	1.196	0.011	0.037
Culmen	1.710	0.005	1.714	0.006	0.027
Declive	1.715	0.002	1.717	0.002	0.001
Fusiform gyrus	1.674	0.001	1.675	0.001	0.015
Lentiform nucleus	1.486	0.012	1.495	0.010	0.017
Lingual gyrus	1.732	0.002	1.736	0.002	0.001
Pyramis	1.468	0.004	1.471	0.005	0.048
Tuber	1.540	0.006	1.543	0.004	0.044
Uncus	1.392	0.003	1.395	0.003	0.001
Uvula	1.508	0.002	1.510	0.003	0.018
Female>male					
Anterior cingulate	1.656	0.007	1.651	0.008	0.036
Culmen of vermis	0.830	0.000	0.830	0.000	0.001
Declive of vermis	0.974	0.000	0.974	0.000	0.001
Medial frontal gyrus	1.790	0.003	1.787	0.004	0.028
Parahippocampal gyrus	1.654	0.001	1.653	0.001	0.012
Postcentral gyrus	1.736	0.007	1.729	0.010	0.005

Pyramis of vermis	0.786	0.000	0.786	0.000	0.001
Superior temporal gyrus	1.809	0.001	1.808	0.002	0.023
Supramarginal gyrus	1.423	0.006	1.418	0.007	0.014
Thalamus	1.652	0.004	1.648	0.006	0.003
Tuber of vermis	0.662	0.000	0.662	0.000	0.001
Uvula of vermis	0.758	0.000	0.758	0.000	0.001

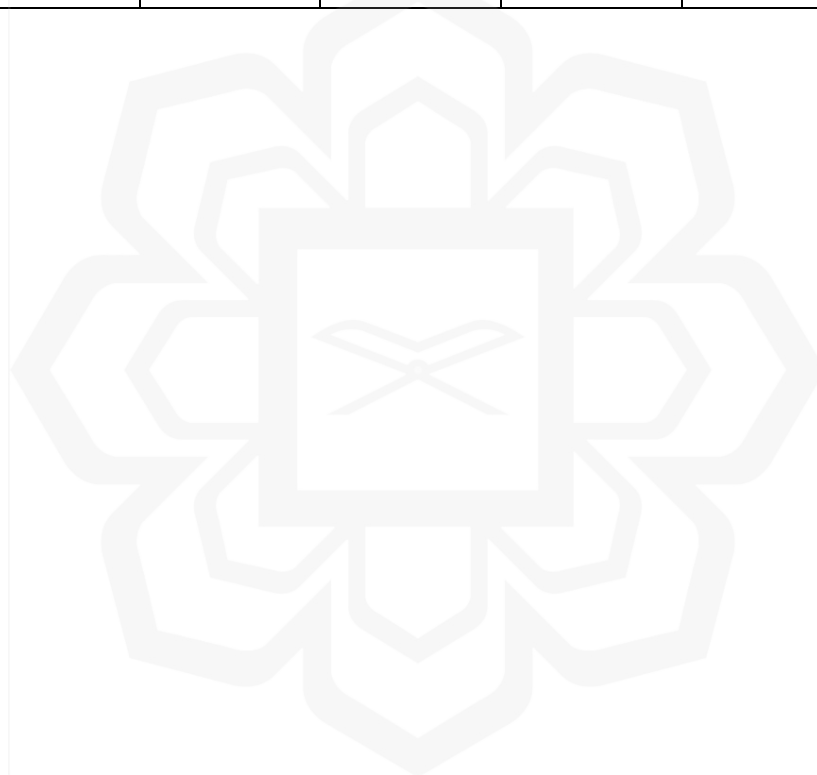


Table 4.6 Box-counting FD- Controlled for Huffaz status.

Brain Region	P-value
Culmen	0.026
Declive	0.005
Fusiform gyrus	0.039
Lentiform nucleus	0.023
Lingual gyrus	0.001
Medial frontal gyrus	0.045
Parahippocampal gyrus	0.014
Postcentral gyrus	0.006
Superior temporal gyrus	0.028
Supramarginal gyrus	0.025
Thalamus	0.002
Uncus	0.004
Uvula	0.019

4.5 STUDY 4: FOURIER FRACTAL DIMENSION ANALYSIS

This section of the results chapter presents the findings from the Fourier fractal dimension (FFD) analysis, which was employed to assess brain complexity in relation to sexual dimorphism. The Fourier method differs from box-counting in that it evaluates the complexity of brain structures by analysing their frequency patterns, offering insight into the spatial distribution of surface features at varying scales. This method decomposes the brain's structural patterns into different frequencies, capturing how detailed and irregular these patterns are across the cortex and subcortical regions.

The FFD provides a complementary view to the box-counting method, offering a more refined understanding of brain complexity by focusing on the frequency domain. In this analysis, the study explored whether males and females differ in terms of fractal complexity, and whether these differences manifest in specific regions of the brain. Similar to previous analyses, the FFD analysis was performed in two directions: identifying regions where males exhibit greater complexity than females, and regions where females show higher complexity than males. This approach adds another layer to the investigation of sexual dimorphism, highlighting not just size differences, but also structural intricacies at a finer, frequency-based level.

The FFD analysis confirmed the sex-related differences identified in the box-counting method, with overlapping results observed in regions such as the lingual gyrus, declive, and medial frontal gyrus. Additionally, the Fourier analysis revealed unique findings, including higher FD values in males within the superior occipital gyrus and in females within the insula and posterior cingulate, which were not detected using the box-counting approach. The results of the FFD analysis are detailed in Table 4.7 and 4.8, encompassing both uncontrolled and Huffaz-controlled conditions. Brain regions exhibiting significant sex differences in fractal dimension (FD) were identified and classified as either male-dominant (higher mean FD in males) or female-dominant (higher mean FD in females).

Notably, the controlled analysis indicated that certain sex-related differences in FD were influenced by Quran memorization; however, key regions, including the inferior occipital gyrus and medial frontal gyrus, consistently demonstrated sex-related differences regardless of cognitive training.

Table 4.7 Fourier FD – Uncontrolled.

Brain region	Female		Male		P-value
	Mean FD	SD	Mean FD	SD	
Male>female					
Superior occipital gyrus	4.178	0.016	4.191	0.020	0.016
Tuber of vermis	4.792	0.002	4.793	0.003	0.007
Female>male					
Anterior cingulate	3.695	0.013	3.687	0.014	0.037
Cerebellar tonsil	3.616	0.024	3.599	0.024	0.023
Declive	3.791	0.013	3.776	0.012	0.001
Inferior semilunar lobule	3.678	0.034	3.657	0.029	0.035
Insula	3.896	0.009	3.890	0.011	0.031
Lingual gyrus	3.743	0.015	3.723	0.016	0.001
Posterior cingulate	3.646	0.011	3.632	0.014	0.001

Table 4.8 Fourier FD - Controlled for Huffaz status

Brain Region	P-value
Anterior cingulate	0.017
Cerebellar tonsil	0.039
Declive	0.001
Inferior occipital gyrus	0.040
Inferior semilunar lobule	0.043
Insula	0.032
Lingual gyrus	0.001
Medial frontal gyrus	0.028
Posterior cingulate	0.001
Superior occipital gyrus	0.018
Tuber of vermis	0.003

4.6 STUDY 5: MACHINE LEARNING-BASED BRAIN SEX CLASSIFICATION

This final section presents the findings which utilized ML techniques to classify brain sex based on structural MRI data. Building upon the volumetric and FD analyses in previous studies, this phase of the research leveraged computational models to enhance the understanding of sexual dimorphism in brain structure. Specifically, the study explored how features such as grey matter volume and FD complexity, derived from MRI scans, could be used to classify sex, and examined the impact of Huffaz status (reflecting intensive cognitive training) on the classification performance.

In this study, four ML algorithms were employed: logistic regression, support vector machine, deep learning, and random forest. These algorithms were selected based on their demonstrated effectiveness in prior neuroimaging research, as highlighted in the systematic review in Chapter 2. The features used for classification were drawn from the volumetric and FD analyses, providing a comprehensive dataset that captured both the size and complexity of brain structures. Importantly, the study also considered the Huffaz status of participants, evaluating how this cognitive training influenced the models' ability to accurately predict sex.

The findings presented in this chapter assess the performance of each ML algorithm in terms of accuracy, sensitivity, specificity, and AUC. The results provide a detailed examination of the structural differences between male and female brains and offer insights into the influence of intensive cognitive training on these differences. Furthermore, the chapter discusses the comparative strengths of the ML models and the role of Huffaz status in modulating brain structure, contributing to the broader understanding of sexual dimorphism in the context of neuroplasticity and cognitive practices.

4.6.1.1 Performance of Machine Learning Models Without Huffaz Status

When the Huffaz status was excluded as a predictor variable, the ML models demonstrated varying degrees of success in classifying sex based solely on structural brain features. As summarized in Table 4.9, the classification accuracy ranged from 42.42% to 84.85%, highlighting the differing capacities of the models to utilize features like brain volume and FDs for sex classification.

- **Logistic Regression** showed the lowest accuracy, with a performance of 42.42% when using the BCFD. This suggests that logistic regression struggled to capture meaningful patterns in the data when relying on this specific feature set, indicating its limitations in modelling complex brain structures.
- **Random Forest and Support Vector Machine**, however, achieved the highest accuracy (84.85%) when utilizing brain volume and a combination of all available features. These results indicate that both models were highly effective in leveraging the structural differences in brain volume to predict sex, affirming the importance of volume as a key discriminative feature.
- **AUC Analysis:** The highest AUC without Huffaz status was recorded by the SVM model using the volume feature, with an AUC value of 0.904. This finding emphasizes the robustness of brain volume as a feature, providing the SVM model with a high discriminative capacity to differentiate between male and female brains based on structural data.
- **Sensitivity and Specificity:** Sensitivity peaked at 84.62%, attained by both the SVM and random forest models when using volume. In contrast, the lowest sensitivity and AUC values (0%) were recorded for the SVM model when applying the BCFD feature, indicating that FD, particularly box-counting, did not contribute significantly to model performance. In terms of specificity, the highest (100%) values were achieved by both the SVM and deep learning models when using FD features. Interestingly, SVM maintained a perfect specificity across all features, which highlights its reliability in correctly

identifying true negatives (i.e., the correct classification of the opposite sex) in the dataset.

- **Lowest Performance:** The poorest specificity (35%) was noted in the logistic regression model when using the BC feature, reinforcing the observation that logistic regression was suboptimal for this classification task when utilizing FD-based features alone.

4.6.1.2 Performance of Machine Learning Models with Huffaz Status

Incorporating Huffaz status as a predictor significantly improved the classification accuracy across the ML models. As shown in Table 4.10, accuracy now ranged from 50% to an impressive 92.86%, indicating that cognitive training associated with Quran memorization plays a key role in amplifying sex-related brain structural differences.

- **Logistic Regression** again showed the lowest accuracy at 50% when utilizing BCFD, reflecting its limited capacity to model sex differences even with the addition of cognitive training as a variable. However, the inclusion of Huffaz status still yielded some improvement over the performance without it, particularly in combination with FD features.
- **Random Forest and Deep Learning Models** achieved the highest accuracy of 92.86%, outperforming all other models when using a combination of all available features, including FD and volume. This result highlights the effectiveness of these models in capitalizing on both brain structure and cognitive training information to enhance the precision of sex classification. These models also recorded the highest AUC value of 0.958, further underscoring their ability to effectively distinguish between sexes when Huffaz status is considered.
- **Sensitivity and Specificity:** The sensitivity of the random forest and deep learning models reached a perfect 100% when combining all features, which

indicates that these models correctly classified all individuals as either male or female. In contrast, the lowest sensitivity and AUC (0%) were again observed in the SVM model when applied to BCFD and both types of FD. This suggests that despite SVM's strong performance with volume, it struggles to derive meaningful patterns from FD features, even with the inclusion of Huffaz status.

- **Specificity:** Perfect specificity (100%) was achieved by the SVM, deep learning, and random forest models when utilizing both FD features. This demonstrates the models' consistent ability to accurately classify the opposite sex when FD features are considered. However, the lowest specificity (37.5%) was noted for the volume feature, suggesting that while volume enhances sensitivity, it may sometimes reduce the ability of models to accurately reject incorrect classifications when Huffaz status is included.

4.6.1.3 Comparative Analysis Between Models

Across all models and feature sets, random forest and deep learning consistently outperformed other ML methods, achieving the highest accuracy and AUC values. This suggests that these models were better able to integrate the complex patterns in brain volume and FDs, especially when the cognitive training status (Huffaz or non-Huffaz) was considered.

Notably, SVM demonstrated strong performance with brain volume, both with and without Huffaz status, but struggled with FD-based features. This observation aligns with prior research (Zhang et al., 2020), which has found that SVM excels with certain types of brain structure data, particularly when it involves clear volumetric differences between males and females.

On the other hand, logistic regression, while a simpler model, performed consistently poorly across all feature sets. Its inability to achieve high accuracy or AUC suggests that it may be ill-suited for complex neuroimaging data that involves multifaceted patterns in brain structure.

4.6.1.4 Feature Analysis

The performance results highlight that brain volume consistently emerged as the most predictive feature for sex classification across models, achieving the highest accuracies and AUC values. Volume features provided a clear structural difference between male and female brains, which models like random forest, SVM, and deep learning could effectively exploit.

In contrast, the analysis of FDs—particularly BCFD—revealed mixed results. FD features generally yielded lower accuracies and AUC values, particularly for models like SVM and logistic regression. However, when combined with volume in models like random forest and deep learning, FD contributed to achieving the highest overall classification performance. This suggests that while FD alone may not be as powerful for sex classification, it provides complementary information that, when integrated with other features, enhances model performance.

Table 4.9 Sex classification performance without Huffaz group as predictor.

Features	Accuracy (%)	AUC	Sensitivity (%)	Specificity (%)
Logistic regression (LR)				
FFD	54.55	0.585	38.46	65
BC	42.42	0.269	53.85	35
Combined FD	54.55	0.585	38.46	65
Volume	63.64	0.773	30.77	85

All features	54.55	0.585	38.46	65
Support vector machine (SVM)				
FFD	69.70	0.742	30.77	95
BC	60.61	0	0	100
Combined FD	60.61	0	0	100
Volume	84.85	0.904	84.62	85
All features	60.61	0	0	100
Deep learning (DL)				
FFD	57.58	0.619	15.38	85
BC	63.64	0.592	15.38	95
Combined FD	66.67	0.746	15.38	100
Volume	75.76	0.858	53.85	90
All features	69.70	0.719	30.77	95
Random forest (RF)				
FFD	66.67	0.656	23.08	95
BC	63.64	0.748	46.15	75
Combined FD	66.67	0.708	38.46	85
Volume	84.85	0.885	84.62	85
All features	84.85	0.879	76.92	90

Note: The value highlighted in bold exhibited the highest level of performance.

Table 4.10 Sex classification performance with Huffaz group as predictor.

Features	Accuracy (%)	AUC	Sensitivity (%)	Specificity (%)
Logistic regression (LR)				
FFD	71.43	0.75	50	87.5
BC	50	0.437	33.33	62.5
Combined FD	71.43	0.75	50	87.5
Volume	57.14	0.375	83.33	37.5
All features	71.43	0.75	50	87.5
Support vector machine (SVM)				
FFD	78.57	0.875	66.67	87.5
BC	57.14	0	0	100
Combined FD	57.14	0	0	100
Volume	85.71	0.896	83.33	87.85
All features	57.14	0	0	100
Deep learning (DL)				
FFD	78.57	0.812	66.67	87.5
BC	78.57	0.792	50	100
Combined FD	78.57	0.75	83.33	87.5
Volume	85.71	0.917	83.33	87.5
All features	92.86	0.958	100	87.5

Random forest (RF)				
FFD	78.57	0.771	83.33	75
BC	85.71	0.958	83.33	87.5
Combined FD	92.86	0.948	83.33	100
Volume	85.71	0.938	83.33	87.5
All features	92.86	0.958	100	87.5

Note: The value highlighted in bold exhibited the highest level of performance.

These findings demonstrate the strong potential of machine learning, particularly random forest and deep learning algorithms, to accurately classify sex based on neuroimaging data, even when accounting for the influence of cognitive practices such as Quran memorization. The variation in performance across algorithms and feature sets highlights the critical role of thoughtful feature selection and model optimization in ensuring robust and accurate classification in neuroimaging studies.

4.7 CONCLUSION

This chapter has presented the key findings from the analyses investigating brain sexual dimorphism and the influence of cognitive training, particularly Quran memorization. The results spanned several areas, including volumetric differences between males and females, complexity analyses using FD methods, and machine learning-based classification techniques. Consistent patterns of sexual dimorphism were observed, with males exhibiting greater grey matter volumes across various brain regions. Furthermore, complexity analyses revealed notable differences in brain structure intricacies, underscoring the potential influence of sex on brain geometry.

ML models, particularly random forest and deep learning algorithms demonstrated high accuracy in classifying brain sex based on these structural features, even when considering the effects of cognitive training. These findings provide a comprehensive view of how brain structure is influenced by sex and cognitive practices, contributing to a deeper understanding of neuroanatomical differences.

The detailed discussion and interpretation of these findings, including their implications for the fields of neuroimaging and cognitive neuroscience, will be elaborated in the following chapter (Chapter 5).



CHAPTER FIVE

DISCUSSION

5.1 INTRODUCTION

This chapter provides a comprehensive interpretation of the key findings presented in the results section, placing them in the broader context of existing research on brain sexual dimorphism and the effects of cognitive training, such as Quran memorization, on brain structure. The discussion will examine the implications of volumetric and complexity differences between males and females, as well as the performance of ML models in classifying brain sex based on these structural features. Additionally, this chapter will address the limitations of the current study, including methodological constraints and sample characteristics, and offer recommendations for future research to enhance our understanding of how sex and cognitive practices shape neuroanatomy. By critically analysing the results and considering potential confounding factors, this chapter aims to provide a nuanced interpretation of the findings and suggest directions for future investigations.

5.2 VOLUMETRY ANALYSIS (STUDY 1 AND STUDY 2)

5.2.1 Sexual Dimorphism in Brain Structure

The volumetry analysis conducted in this study provides a robust examination of sex-related differences in brain structure, with results drawn from both VBM and VOI analyses. Our findings strongly support the view that there are significant differences in brain volume between males and females, aligning with numerous studies that have documented sex-related variations in brain structure. Specifically, our findings demonstrated that males

consistently exhibited larger grey matter volumes in key brain regions, including the cerebellum, temporal gyrus, fusiform gyrus, parahippocampal gyrus, and hippocampus. These findings align with existing literature which reported similar patterns of sexual dimorphism across these regions (Del Mauro et al., 2022; Lotze et al., 2019; Ruigrok et al., 2014). These results challenge the alternative perspective that both sexes have indistinguishable brain structures, emphasizing that there are indeed distinct neuroanatomical differences that must be considered when studying brain morphology (Joel, 2021; Joel et al., 2018, 2020).

The VOI analysis, utilizing five distinct probabilistic brain atlases (Neuromorphometrics, LPBA40, TD, CoBrA, and SUI), confirmed the overall trend of larger male brain volumes across both cortical and subcortical structures. This analysis revealed additional sex differences in specific regions, including the frontal, temporal, parietal, and occipital lobes, which align with the findings of Allen et al. (2003) and Del Mauro et al. (2022). Notably, while our VBM analysis—corrected for total intracranial volume—indicated larger male volumes predominantly in temporo-occipital regions, Del Mauro et al. (2022) observed a similar pattern after adjusted to total brain volume, where males showed larger volumes in temporo-occipital areas, while females exhibited larger volumes in fronto-parietal regions.

Subcortical volumetric analyses further confirmed the presence of sexual dimorphism, with males exhibiting larger volumes in the cerebellum, and hippocampus, consistent with findings by Ruigrok et al. (2014). Our study is among the first to identify significant sex differences in cerebellar lobules using both anatomical (CoBrA, TD, LPBA40) and zonal (SUI, Neuromorphometrics) divisions. Additionally, this study is the first to report sexual dimorphism in the dentate gyrus and subiculum, components of the hippocampus, as revealed by the CoBrA atlas.

Within the basal ganglia, our analyses utilizing CoBrA and TD atlases revealed that males exhibited larger globus pallidus volumes, corroborating the earlier findings by Rijpkema et al. (2012). Additionally, the TD atlas identified volumetric differences in the subthalamic nucleus, aligning with the findings of Tugcu et al. (2023), further supporting the presence of sexual dimorphism in this tiny region. Notably, this study is the first to

document sex-based volumetric differences in striatal volume using the CoBrA atlas, potentially contributing to understanding previously reported sex differences in striatal dopamine regulation (Zachry et al., 2021). Furthermore, our analysis identified significant sex differences in the hypothalamus, echoing findings by Makris et al. (2013), who utilized 7T MRI to demonstrate larger hypothalamic volumes in males.

Overall, our results are consistent with previous studies, confirming that males generally exhibit larger overall brain volumes than females. This difference ranged from 9.74% to 12.41% across the various atlases employed in this study: Neuromorphometrics (10.42%), LPBA40 (9.95%), TD (9.74%), CoBrA (11.66%), and SUIT (12.41%). These findings align with the meta-analysis conducted by Ruigrok et al. (2014), which reported that males exhibit 8-13% larger total brain volumes than females.

5.2.2 Impact of Cognitive Training on Sexual Dimorphism

In addition to identifying widespread sex differences in brain structure, this study also explored the impact of intensive cognitive training on these differences. Specifically, we investigated the role of Quran memorization (Huffaz status) as a modulating factor in brain sexual dimorphism. The VBM analysis revealed that controlling for Huffaz status unveiled additional sex-related differences in regions such as hypothalamus, amygdala, lingual gyrus, and cingulate cortex. These findings align with Jamaludin et al. (2022) that found significant areas between Huffaz and non-Huffaz, which suggested that the rigorous memorization process undertaken by Huffaz during their 18-month training program may induce neuroplastic changes, potentially amplifying inherent sexual dimorphism.

The additional sex differences observed after adjusting for Huffaz status raise intriguing questions regarding the interplay between biological sex, neuroplasticity, and cognitive training. Specifically, the fact that these differences became apparent only after considering the effects of cognitive training suggests that intensive memorization practices may differentially impact brain structure in males and females. The regions identified—such as the caudate nucleus and putamen—are known to be involved in cognitive functions

such as memory, learning, and motor control, indicating that these areas may be particularly sensitive to the effects of prolonged cognitive training (Grahm et al., 2008).

Moreover, VOI analysis across the five brain atlases confirmed that even after controlling for Huffaz status, significant male-female differences remained, particularly in areas associated with memory and cognitive processing. These results provide further evidence that cognitive training, while influential, may not entirely account for the observed sex differences in brain volume. Instead, the interplay between sex and cognitive training may reflect a complex interaction between biology and experience, with both contributing to the observed patterns of brain structure.

5.2.3 Methodological Considerations

The observed variability in sex differences across our VBM and VOI analyses, as well as in other previous studies, underscores the methodological discrepancies between these approaches and their potential influence on results. As highlighted by Seyedi et al. (2020), VBM detects structural differences at the voxel level, offering a more detailed, voxel-wise analysis, while VOI focuses on predefined brain regions, potentially leading to divergent outcomes. Furthermore, the plethora of published methods and metrics for studying brain volume, as noted by Zhou et al. (2022), may contribute to variability in findings across studies.

The choice of brain atlas can introduce variability, particularly in VOI analysis, due to several factors. For instance, research has shown potential biases and localization errors when applying atlases derived from Western populations to Chinese populations (Liang et al., 2015). Furthermore, Evans et al. (2012) emphasized the importance of considering variables such as age, sex, hemispheric asymmetry, anatomical correspondence, spatial normalization methods, and disease specificity when selecting an appropriate atlas template and mapping function. Additionally, the lack of a standardized definition for VOI boundaries can lead to inconsistencies and difficulties when comparing findings across studies (Cox et al., 2014). Our study's focus on a single ethnicity, Malay individuals in

Malaysia, for which no dedicated brain atlas exists, further emphasizes the potential limitations in generalizability and the need for developing population-specific atlases. Nevertheless, by leveraging the unique strengths of multiple atlases, our study provides a more comprehensive and nuanced understanding of sexual dimorphism in the brain. This multi-atlas approach allows for the identification of regions that may be significant in one atlas but not in another, thereby offering a more detailed map of sex-related brain differences.

5.2.4 Limitation

Our study's volumetric analysis, specifically the VOI approach, exclusively utilized absolute brain volume measurements without adjusting for brain size. While the influence of brain size on brain volume remains a topic of ongoing debate in the field of neuroimaging, there is evidence to suggest that adjusting brain size may offer a more precise understanding of sex-related differences. Previous research, such as the work by Del Mauro et al. (2022), has demonstrated that accounting for variations in total brain volume can refine the interpretation of brain size differences between males and females, particularly in cases where sex differences in brain volume may be partly influenced by overall brain size rather than inherent neuroanatomical characteristics.

However, it is important to note that our VBM analysis was corrected for total intracranial volume, which is also a method for controlling for overall brain size. This correction helps to ensure that observed differences in brain volume are more likely to reflect true neuroanatomical variations rather than being confounded by individual differences in head or brain size. Future VOI studies should consider incorporating adjustments for these factors to provide a more comprehensive understanding of sex-related brain differences. This would allow for a more nuanced exploration of how biological and environmental variables, such as body size, may interact with neuroanatomical characteristics to influence brain volume.

5.3 COMPLEXITY INDEX ANALYSIS (STUDY 3 AND STUDY 4)

5.3.1 Fractal Dimension and Sex-Related Differences in Brain Complexity

The primary aim of this study was to explore the potential of FD analysis in uncovering subtle sex-related differences in brain morphology. It is hypothesized that FD, a measure of structural complexity, could reveal nuanced variations in brain organization between males and females. To test this hypothesis, two distinct FD estimation methods—box-counting and Fourier analysis were employed—targeting both cortical and subcortical brain regions in a cohort of healthy young adults. Additionally, the influence of intensive memorization practices by comparing FD between Huffaz (individuals who have memorized the entire Quran) and non-Huffaz participants were explored. This multi-dimensional approach aimed to elucidate the complex interplay between sex, cognitive training, and brain structure, offering novel insights into the neurobiological foundations of sex-related differences in cognition and behaviour.

Firstly, our findings on brain complexity enhance the argument that there are significant differences in brain volume between males and females by demonstrating that sex differences extend beyond mere volumetric measures. The complexity analysis, which examined the intricate patterns of cortical folding, revealed additional nuances that differentiate male and female brains, with males and females showing distinct complexity in regions like the medial frontal gyrus and lingual gyrus. These results provide further evidence that the structural differences between the sexes are not just a matter of size but also involve more subtle, intricate features of brain organization, thus reinforcing the hypothesis that male and female brains are structurally distinct.

5.3.2 Key Regions of Complexity Differences

The convergence of findings from both box-counting and Fourier FD analyses identified several key regions, including the declive, lingual gyrus, and medial frontal gyrus, as exhibiting robust sex-related differences in brain complexity. These differences persisted even after controlling for the potential influence of intensive memorization practices, suggesting that these regions play a significant role in contributing to sex-related brain complexity. The fact that these regions were consistently highlighted across both box-counting and Fourier FD methods further reinforces their importance in understanding the structural intricacies underlying brain sexual dimorphism.

5.3.3 Persistent and Modulated Differences After Controlling for Huffaz

The FD analyses, utilizing both box-counting and Fourier methods, unveiled a complex interplay between sex, cognitive practice, and brain complexity. Initially, numerous brain regions exhibited sex-related differences in FD, some of which persisted even after controlling for the influence of Huffaz status. Regions such as the fusiform gyrus, lentiform nucleus, and lingual gyrus demonstrated higher FD in males across both analyses, while females exhibited higher FD in regions including the medial frontal gyrus, parahippocampal gyrus, postcentral gyrus, and superior temporal gyrus. Notably, some of these sex differences disappeared after controlling for Huffaz status, indicating that intensive memorization practices may modulate brain complexity in a sex-dependent manner. This finding highlights the dynamic interplay between cognitive engagement and inherent sex-related differences in brain organization.

5.3.4 Comparison Between Box-Counting and Fourier FD Analysis

The FFD analysis provided additional layers of understanding by revealing sex-related variations in regions such as the inferior occipital gyrus and medial frontal gyrus after controlling for Huffaz status. This underscores the value of employing multiple methods to capture a more comprehensive picture of brain complexity. Male-dominant regions identified through FFD included the superior occipital gyrus and tuber of vermis, while female-dominant regions included the anterior cingulate, cerebellar tonsil, declive, and insula. Interestingly, the lingual gyrus and declive showed contrasting patterns between methods, with box-counting revealing higher FD in males and Fourier FD suggesting greater complexity in females. This discrepancy underscores the need for further investigation to determine how different FD estimation methods may capture distinct aspects of brain complexity, such as space-filling properties versus spatial frequency distribution.

5.3.5 Comparison with Recent Literature

The findings of this study align and contrast with recent investigations into brain complexity and sexual dimorphism. Chen et al. (2023) utilized spherical harmonic reconstructions to estimate FD in a large Chinese population and observed regional differences in FD that varied by sex. In contrast to our findings, they reported lower FD in females in the right inferior parietal lobule and postcentral gyrus, though their analysis also revealed female dominance in the lingual gyrus and rostral middle frontal gyrus. Similarly, Del Mauro et al. (2022) reported higher FD in males across the whole brain in a young adult population. However, the study by (Liu et al., 2020), focusing on an older cohort, observed greater FD in males within the left thalamus and bilateral amygdala, suggesting that aging may influence sex-related differences in brain complexity.

The observed discrepancies between our findings and these studies may stem from variations in sample characteristics, such as population genetics and age, as well as the

methodological differences in FD estimation techniques. For instance, while this study employed box-counting and Fourier FD methods, other studies utilized spherical harmonic reconstructions, which assess cortical surface complexity based on different mathematical principles. The differences in these approaches may capture different facets of brain complexity, further contributing to the observed variability in sex-related differences across studies.

5.3.6 The Role of the Lingual Gyrus in Sex Differences

The lingual gyrus emerged as a region of particular interest in both our analyses and the literature. While our box-counting analysis indicated higher FD in males, the Fourier analysis suggested greater complexity in females. The prominence of the lingual gyrus in both analyses, coupled with its importance in visual processing and language functions, indicates that it may be a critical region for understanding sex-related differences in brain complexity. Further research is needed to determine the neuroanatomical and functional correlates of these differences, particularly in relation to cognitive and behavioural sex differences.

5.3.7 Limitation

This study faced several limitations, particularly in the context of the FD analysis. One of the primary challenges stems from the scarcity of research specifically investigating sex differences in brain complexity using FD. The limited body of literature on this topic makes it difficult to draw definitive conclusions and situate our findings within a broader scientific context. The relative novelty of using FD to measure brain complexity, particularly in the study of sexual dimorphism, leaves open many questions about how these differences manifest across populations and cognitive domains. Without a substantial number of studies for comparison, interpreting the results of FD analysis and generalizing them is more complex.

Additionally, variation in FD techniques presents another significant limitation. This study employed both box-counting and Fourier FD methods, but there is considerable diversity in how FD can be computed in neuroimaging research. For example, while this study utilized box-counting and Fourier FD, recent research by Chen (2023) employed spherical harmonic reconstructions to compute FD. The different techniques for FD calculation make cross-study comparisons challenging, as each method may capture different aspects of brain complexity, leading to variations in findings. This diversity in FD methodology highlights the need for a more standardized approach in future research to enable better comparison and interpretation of results across studies.

Despite these limitations, this study contributes to the current understanding of brain complexity, particularly regarding the simplest complexity measure—box-counting FD. The results extend the knowledge of how brain complexity can be quantified and the role it plays in distinguishing sex-related differences in brain structure. However, more studies are needed to explore the effects of using different FD techniques. Future research should investigate the impact of various FD calculation methods, such as spherical harmonic reconstructions and others, to determine how these approaches compare and what additional insights they might offer into brain structure and complexity. Establishing a more unified framework for FD analysis will be essential for advancing the study of brain complexity and understanding its role in neuroanatomical differences between males and females.

5.4 BRAIN SEX CLASSIFICATION TECHNIQUE (STUDY 5)

The present study aimed to classify sex using ML methods by leveraging structural features of the brain, specifically FD and volume measurements. The central hypothesis driving this research was that brain structure could serve as a reliable biomarker for sex classification, and that cognitive training, as seen in Huffaz, may influence the neuroanatomical features related to sex differentiation. The findings strongly support the hypothesis, particularly when incorporating Huffaz status, suggesting that cognitive training plays a role in

amplifying sex-related differences in brain structure. The integration of these structural features into ML models resulted in high classification accuracy, with substantial improvements when considering the influence of the Huffaz group.

5.4.1 Accuracy of Machine Learning Models Without Huffaz Status

In the absence of Huffaz status as a predictor, the random forest and support vector machine models demonstrated the highest levels of accuracy. Specifically, the random forest model achieved an accuracy of 84.85% when using brain volume features, which was mirrored by the SVM model. These results highlight the robustness of brain volume as a feature for sex classification, supporting the view that structural differences between male and female brains are sufficiently distinct for ML algorithms to distinguish between the sexes. The highest AUC achieved without the inclusion of Huffaz status was 0.904, again attained by the SVM model using volume. This high AUC underscores the discriminative power of volume-based features, confirming their utility in sex classification tasks.

5.4.2 Impact of Huffaz Status on Model Performance

When Huffaz status was introduced as a predictor, the performance of the ML models significantly improved, particularly for the random forest and deep learning models. The highest accuracy, 92.86%, was achieved by these models when utilizing a combination of all features, including both FD and volume. Additionally, these models recorded the highest AUC of 0.958, further emphasizing their ability to effectively classify sex when Huffaz status is accounted for.

The inclusion of Huffaz status suggests that Quran memorization—a cognitively demanding practice—may induce neuroanatomical changes that enhance the differences in brain structure between males and females. This aligns with prior research on brain plasticity, which indicates that intensive memory training can lead to structural alterations

in specific regions of the brain, particularly those associated with memory and cognitive functions (Jamaludin et al., 2022). In the context of sex classification, these neuroplastic changes may amplify sex-related structural differences, making it easier for ML models to distinguish between male and female brains with greater precision.

5.4.3 Comparative Analysis with Previous Research

Our findings are consistent with previous studies that have applied ML techniques to sex classification based on brain imaging data. For example, earlier research reported classification accuracies of up to 90% using SVM, particularly when focusing on brain volume as a key feature (Sanchis-Segura et al., 2022). Similarly, our study demonstrated that the random forest and SVM models using volume features alone could achieve a high accuracy of 84.85%. The improvement in accuracy to 92.86% when including the Huffaz group highlights the importance of incorporating additional features—such as cognitive training status—to refine classification performance.

Volume, as a robust and highly discriminatory feature, consistently yielded superior accuracy across most ML models, with or without the inclusion of Huffaz status. This finding is consistent with prior research, which has shown that volume-based features tend to perform well in ML models for sex classification (Sanchis-Segura et al., 2022; L. Wang et al., 2012; X. Yang et al., 2021; Zhang et al., 2020). In contrast, FD analysis, while offering complementary insights into the complexity of brain surface geometry, demonstrated relatively lower accuracy. This finding aligns with existing literature, which has shown that FD, though informative, may capture more subtle aspects of brain structure that are less influential for sex classification tasks (Ge et al., 2021). This may suggest that while FD provides valuable insights into brain complexity, it may not be as strong a predictor for sex classification as volumetric features when used in isolation hence emphasizing the importance of multimodal feature integration for enhancing sex classification that will discuss in the next subsection.

5.4.4 Feature Integration and Model Optimization

One of the key contributions of this study is the demonstration that combining multiple features—specifically FD and volume—enhances the accuracy of ML models. The random forest and deep learning models performed particularly well when integrating these features, achieving the highest classification accuracy of 92.86%. This supports the growing body of research that advocates for the integration of various structural and functional MRI features to improve classification outcomes (Feis et al., 2013; L. Wang et al., 2012; Weber et al., 2022; Zhang et al., 2020).

Even when Huffaz status was not considered, the random forest model still maintained an impressive accuracy of 84.85%, further affirming the model's robustness in handling diverse brain features. These findings suggest that, while individual features like volume can provide a strong foundation for sex classification, the inclusion of additional features such as FD, and considerations like cognitive training, significantly enhance the discriminative power of ML models. This also aligns with the broader ML literature, where feature engineering and integration are often key to achieving superior model performance.

5.4.5 Limitation

While the findings of this study provide valuable insights into the use of ML for sex classification based on brain structural features, several limitations must be acknowledged. One key limitation is the relatively small sample size, which may affect the robustness and generalizability of the results. ML models, particularly deep learning algorithms, typically benefit from larger datasets that allow them to learn more complex patterns in the data. The small sample size in this study may limit the ability of the models to fully generalize to broader populations, raising the possibility of overfitting. As such, future studies should aim to include larger and more diverse cohorts to validate the findings and improve the external validity of the models.

Additionally, the narrow age range and the focus on a specific population—Malay individuals within Malaysia—could further limit the generalizability of these findings to other ethnic or age groups. Given the documented variability in brain structure across different populations, expanding the sample to include participants from diverse demographic backgrounds will be essential for testing the robustness of the ML models and the observed sex differences across different groups.

In conclusion, while the small sample size and specific population used in this study present limitations, the results still offer valuable preliminary evidence of the potential for ML to classify sex based on brain structural features. Future research should address these limitations by employing larger, more diverse datasets to further improve the accuracy and generalizability of the models.

5.5 GENERAL LIMITATION

Despite the valuable insights gained from this research, several general limitations must be acknowledged. First, the study primarily focused on a young adult population with a relatively small sample size, which could limit the generalizability of the findings. While the sample size was sufficient to explore the intended population of young adults and provided meaningful results within this demographic, larger sample sizes could enhance the robustness of the conclusions. Additionally, the participants in this study were exclusively Malay individuals from Malaysia, limiting the applicability of the findings to other populations. Given the well-documented variability in brain structure across different racial and ethnic groups, influenced by genetic, environmental, and cultural factors (Atilano-Barbosa & Barrios, 2023), the results may not fully capture the diversity of brain sexual dimorphism. Nonetheless, despite these limitations, the findings of this research remain valid, as the sample size was sufficient to reveal significant sex-related differences in brain structure among young adults. The study successfully demonstrated the existence of sexual dimorphism, providing a solid foundation for future investigations across broader populations.

CHAPTER SIX

CONCLUSION

6.1 KEY FINDINGS

This thesis set out to explore the structural and complexity-based differences in brain morphology between males and females, employing a combination of volumetric and FD analyses, and to examine the impact of cognitive training—specifically Quran memorization by Huffaz—on these sex-related differences. Through the application of advanced neuroimaging techniques and ML algorithms, this research provides novel insights into the nature of brain sexual dimorphism and how intensive cognitive practices might modulate these differences. The results of this study have significant implications for understanding sex-related brain organization, the role of cognitive training in neuroplasticity, and the use of ML in neuroimaging research.

One of the primary findings of this study was the consistent evidence of sexual dimorphism in brain structure, particularly in regions such as the cerebellum, hippocampus, amygdala, and fusiform gyrus. Males generally exhibited larger volumes across these regions, aligning with existing literature on brain volume differences between the sexes. These findings contribute to the growing body of knowledge on sex-related differences in neuroanatomy and underscore the importance of considering sex as a biological variable in brain research.

Additionally, this thesis incorporated complexity measurements (FD analysis) to complement volumetric findings, providing a more detailed understanding of brain morphology. The FD analysis revealed nuanced differences in brain structure that may not have been captured through volumetric measures alone, particularly in regions such as the lingual gyrus and medial frontal gyrus, which exhibited contrasting complexity patterns between males and females. The use of both volumetric and complexity analyses highlights

the multifaceted nature of brain structure and the value of using complementary methods to obtain a more comprehensive understanding of sexual dimorphism.

The use of ML methods to classify sex based on brain structural features proved to be highly effective, especially when combining volumetric and FD features. The integration of these multiple features allowed the models to capture a more comprehensive set of structural differences between male and female brains. In the absence of Huffaz status as a predictor, the random forest and support vector machine models demonstrated the highest levels of accuracy. Specifically, the random forest model achieved an accuracy of 84.85% when using brain volume features alone, a result that was mirrored by the SVM model. These findings suggest that brain volume remains a strong and reliable predictor for sex classification, and ML models can effectively leverage these structural features to distinguish between the sexes with high precision. Moreover, the ability of both the random forest and SVM models to achieve similar levels of accuracy reinforces the robustness of volumetric features in sex classification tasks, even without considering additional factors like cognitive training.

The influence of cognitive training, specifically Quran memorization, on brain structure also emerged as an important finding. Controlling for Huffaz status in volumetry analysis revealed additional sex differences in regions such as the calcarine cortex, caudate nucleus, putamen, cuneus, and cingulate cortex. These findings raise intriguing questions about the interplay between cognitive training, neuroplasticity, and inherent sex-related brain differences, emphasizing the role of experience and cognitive engagement in shaping brain structure.

The FD analyses, utilizing both box-counting and Fourier methods, unveiled a complex interplay between sex, cognitive practice, and brain complexity. Initially, numerous brain regions exhibited sex-related differences in FD, some of which persisted even after controlling for the influence of Huffaz status. Regions such as the fusiform gyrus, lentiform nucleus, and lingual gyrus demonstrated higher FD in males across both analyses, while females exhibited higher FD in regions including the medial frontal gyrus, parahippocampal gyrus, postcentral gyrus, and superior temporal gyrus. Notably, some of these sex differences disappeared after controlling for Huffaz status, indicating that

intensive memorization practices may modulate brain complexity in a sex-dependent manner. This finding highlights the dynamic interplay between cognitive engagement and inherent sex-related differences in brain organization.

In terms of machine learning, incorporating Huffaz status led to increased accuracy levels of 92.86% with the random forest and deep learning models, highlighting their superior performance when cognitive training was considered. These findings support the growing application of ML in neuroimaging research, offering a robust tool for exploring complex patterns in brain structure and the cognitive effects on brain plasticity.

6.2 IMPLICATIONS OF THE STUDY

This study makes significant contributions to the field of neuroimaging by providing a deeper understanding of sexual dimorphism in brain structure and the potential impact of cognitive training on brain organization. By integrating both volumetric and complexity-based analyses, the research offers a more nuanced perspective on how sex differences manifest in brain morphology. These methods highlight not only the structural differences in brain volume but also the complexity of brain surface geometry between males and females. This dual approach represents a more comprehensive examination of brain architecture, contributing to the broader discourse on brain sexual dimorphism.

Furthermore, the study underscores the potential of ML as a transformative tool in neuroimaging research. The ability of ML models, such as random forest and support vector machines, to accurately classify sex based on brain structural features demonstrates the power of these techniques to capture subtle patterns in brain data. ML offers a scalable and robust method for analysing large neuroimaging datasets, providing greater precision in identifying sex-based differences and offering insights that might be missed using traditional statistical methods. This positions ML as a crucial instrument for future neuroimaging studies, potentially advancing our understanding of the structural correlates of sex differences and cognitive functions.

The findings of this research also have broader implications for understanding the relationship between cognitive training and brain plasticity. The identification of specific brain regions—such as the calcarine cortex, caudate nucleus, and fusiform gyrus—that exhibit sex-specific differences after controlling for Huffaz status suggests that intensive cognitive practices, such as Quran memorization, may have differential effects on male and female brains. This highlights the modifiable nature of brain structure and supports the idea that cognitive experiences, such as memorization and learning, can reshape brain organization in a sex-dependent manner.

Moreover, these insights have potential applications in education, cognitive training, and neurorehabilitation. The study's findings suggest that cognitive training programmes could be tailored to leverage sex-specific brain plasticity, leading to more effective and personalized educational strategies. For instance, understanding how different types of learning practices impact male and female brains differently could inform the design of targeted interventions to enhance learning outcomes or rehabilitate cognitive deficits. In this way, the study opens the door to further exploration of how tailored cognitive training might optimize brain development and function across different sexes and cognitive domains. This could have lasting impacts not only in academia but also in practical settings such as schools, therapeutic programmes, and cognitive health interventions.

6.3 RECOMMENDATIONS FOR FUTURE RESEARCH

While this study offers valuable insights, several avenues for future research are recommended to build on these findings and address the limitations identified:

6.3.1 Larger and More Diverse Samples

Future studies should aim to involve larger sample sizes and include participants from diverse racial, ethnic, and cultural backgrounds to improve the generalizability of the findings across a wider spectrum of the population. A more diverse participant pool would allow researchers to explore whether the structural brain differences identified in this study are consistent across different genetic and environmental contexts or if specific cultural or racial factors influence the degree of sexual dimorphism. Additionally, expanding the age range to include both younger and older participants would provide valuable insights into how sexual dimorphism in brain structure evolves across the lifespan. Such an approach would enable the study of developmental changes during critical periods, such as childhood and adolescence, as well as the effects of aging on sex-related brain differences. This could help identify potential shifts in brain structure due to hormonal changes, cognitive decline, or age-related neuroplasticity, ultimately contributing to a more comprehensive understanding of how sex differences in the brain manifest and change throughout different life stages. Moreover, a longitudinal design following individuals over time would be beneficial in tracking how cognitive training, such as Quranic memorization, interacts with age and brain structure to influence neural development and maintenance across various phases of life.

6.3.2 Longitudinal Studies

Longitudinal research could provide critical insights into how brain structure changes over time, particularly in response to cognitive training or other experiential factors. By tracking individuals over extended periods, researchers would be able to observe how brain morphology adapts to sustained cognitive practices such as Quranic memorization or other intensive learning activities. This would allow for the identification of key stages in which neuroplasticity, the brain's ability to reorganize and form new neural connections, occurs most prominently in relation to sex-specific differences. Additionally, such studies could reveal how the brain's structural changes are influenced not only by biological factors like sex but also by environmental and cognitive stimuli. This could ultimately shed light on the mechanisms underlying sex differences in neuroplasticity and how these differences manifest over time. Moreover, longitudinal designs would help determine whether the effects of cognitive training are temporary or result in long-lasting alterations to brain morphology, providing a clearer understanding of how sustained mental engagement contributes to brain development and maintenance across the lifespan.

6.3.3 Inclusion of Huffaz Trainees Group

Future research should expand the sample population to include individuals who are currently undergoing Quranic memorization, rather than just those who have completed it. This would allow for a longitudinal analysis of how cognitive training associated with Quranic memorization affects brain structure over time, offering insights into the dynamic nature of brain plasticity during the memorization process. By capturing structural changes at various stages of the memorization journey, researchers can better understand how incremental cognitive training influences sex-related brain differences. Additionally, including this population would provide a more nuanced perspective on the neural correlates of Quranic memorization, potentially identifying specific periods of heightened brain plasticity and their relation to sex classification performance in ML models.

6.3.4 Functional MRI (fMRI) and Connectivity Studies

Future research should also focus on investigating the functional and connectivity changes in the brain by employing techniques such as resting-state functional MRI (fMRI), task-based fMRI, and diffusion tensor imaging (DTI). These advanced neuroimaging techniques would enable researchers to examine how sex-related differences in brain structure influence functional connectivity patterns and cognitive performance. Resting-state fMRI could help identify intrinsic functional networks that may vary between males and females, providing insights into the default modes of brain activity that could underlie sex-based cognitive or behavioural differences. Similarly, task-based fMRI would allow for a more dynamic exploration of how the brain responds to specific cognitive tasks and whether these responses differ between sexes. DTI, on the other hand, could help map the structural integrity of white matter tracts, offering a detailed understanding of the neural pathways that support communication between different brain regions. By combining structural, functional, and connectivity analyses, future studies would provide a more comprehensive view of sexual dimorphism in the brain, helping to bridge the gap between observed anatomical differences and their functional implications in cognition and behaviour.

6.3.5 Feature Integration Approaches

As suggested in our study, feature integration can play a crucial role in increasing the accuracy of sex classification models. By combining multiple features from functional, connectivity, and structural MRI—such as cortical thickness, surface area, and other metrics derived from different MRI sequences—classification models can capture a more holistic view of brain architecture and functionality. The integration of these diverse features allows for a more comprehensive analysis, as each feature provides unique insights into different aspects of brain morphology and activity. For instance, structural features like cortical thickness and surface area can reflect anatomical differences between sexes, while

functional and connectivity metrics offer a window into how these anatomical differences translate into varied patterns of brain activity and communication. This multimodal approach can significantly improve the predictive power of ML models, leading to more accurate sex classification and a deeper understanding of sex-related brain differences. Such advancements in modelling and understanding can contribute to broader applications, including personalized medicine, cognitive research, and the study of brain disorders that exhibit sex-specific characteristics.

6.3.6 Machine Learning for Enhanced Data and Feature Extraction

Future research could leverage ML not only for classification purposes but also for extracting more detailed or previously unnoticed features from brain imaging data. By applying advanced ML algorithms, researchers could uncover hidden patterns or subtle variations in brain structure that may not be apparent through traditional methods of analysis. These algorithms can identify key features that play a critical role in sex differentiation, enabling a more in-depth understanding of how neuroanatomical variations contribute to cognitive and behavioural differences between males and females.

Moreover, applying ML techniques to analyse large-scale, multimodal datasets—incorporating data from functional, structural, and connectivity-based MRI—could greatly enhance the precision and accuracy of classification models. This approach would allow for the integration of diverse data types, thereby providing a more comprehensive picture of sex-related brain differences. Such methods would not only improve classification accuracy but also offer nuanced insights into how various brain features, such as cortical thickness, surface area, white matter integrity, and functional connectivity, interact to create sex-specific neural signatures.

Expanding the dataset to include additional neuroanatomical, cognitive, or behavioural features could further enhance the robustness and generalizability of ML models. This would allow researchers to develop models that perform well across different populations and cognitive contexts, thereby offering a more global understanding of brain

sexual dimorphism. As datasets grow in complexity and scale, ML will play an increasingly vital role in parsing these intricate patterns, ultimately contributing to more personalized and sex-informed approaches to neuroscience and clinical interventions.

6.3.7 Investigating the Role of Other Cognitive Domains

Beyond Quran memorization, future studies could investigate the impact of other forms of cognitive training or learning paradigms on brain structure. This could include activities such as language learning, musical training, or problem-solving exercises, which may influence brain organization in distinct ways. By broadening the scope to encompass various learning methods, researchers would gain a more comprehensive understanding of how different types of cognitive engagement affect brain plasticity across sexes. Additionally, exploring the interaction between cognitive training and sex-specific brain adaptations could offer valuable insights into how male and female brains respond differently to new cognitive demands.

This research could inform the development of customized learning methods tailored to the unique cognitive strengths and structural differences between males and females. Understanding how each sex optimally learns, and processes information could lead to more effective educational strategies, training programmes, and interventions that align with the natural learning tendencies of both men and women. These findings could be particularly useful in fields such as education, cognitive development, and rehabilitation, where sex-specific approaches might maximize learning outcomes and cognitive enhancement.

6.3.8 Multiple FD analysis techniques

Additionally, incorporating more advanced FD estimation techniques, such as spherical harmonic reconstructions, could provide a more comprehensive understanding of brain complexity by capturing different aspects of cortical folding and organization. Further investigation is also needed to explore the functional implications of sex-related differences

in brain complexity, particularly in regions like the lingual gyrus and declive, where the findings diverge across FD estimation methods.

6.4 CONCLUSION

In conclusion, this thesis provides compelling evidence for sex-related differences in brain structure, demonstrating the value of integrating both volumetric and complexity-based analyses to capture a more comprehensive picture of brain sexual dimorphism. By leveraging multiple features such as brain volume and FDs, the study was able to highlight how structural brain differences between males and females can be accurately classified using ML models. The results underscore the importance of cognitive training—such as Quran memorization—as a significant factor influencing brain morphology, revealing that intensive cognitive practices can amplify these sex-related differences.

Furthermore, the application of ML in this research has proven to be a powerful tool, enabling not only accurate classification but also the potential for uncovering hidden patterns in brain structure that might otherwise remain unnoticed through conventional analysis. This approach bridges the gap between observable anatomical differences and the cognitive or functional implications of these differences, making it a promising avenue for future research.

While this study has advanced our understanding of brain sexual dimorphism and the effects of cognitive training, there are several areas for further exploration. Future research should focus on expanding sample populations to be more diverse in terms of race, ethnicity, and age to improve the generalizability of the findings. Longitudinal studies are especially important for tracking brain changes over time, allowing for a deeper understanding of how cognitive training impacts brain development and structural adaptation. Incorporating functional and connectivity-based MRI data could further enhance the accuracy of sex classification models and provide more detailed insights into how structural differences translate into variations in brain function.

Lastly, future studies should consider exploring different forms of cognitive training beyond Quran memorization to investigate how various types of learning affect brain structure in both males and females. This could pave the way for the development of customized learning methods that consider the cognitive strengths and neural plasticity of each sex, ultimately contributing to more personalized approaches in education, cognitive therapy, and brain health interventions.



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APPENDIX I: ETHICAL APPROVAL

 الجامعة الإسلامية العالمية ماليزيا INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA Garden of Knowledge and Virtue		LEADING THE WAY KHALIFAH • AMANAH • IQRA' • RAHMATAN LIL'ALAMIN SUSTAINABILITY INSTITUTION OF THE YEAR
RESEARCH MANAGEMENT CENTRE (RMC)		
Our Ref. :	IIUM/504/14/11/2/ IREC2024-040	
Date :	26 March 2024	
Prof. Dr. Mohd Zulfaezal Che Azemin (Principal Investigator) Kulliyah of Allied Health Sciences IIUM Kuantan Campus		
Dear Prof. Dr.,		
The IIUM Research Ethics Committee (IREC) has reviewed your study protocol as mentioned below:—		
ID NO.	: IREC2024-040	
RESEARCH TITLE	: Gender Differences In Brain Morphology: A Volume Of Interest-Based Fractal Analysis Approach And Logistic Regression Modelling Of Structural MRI Data	
REGISTRATION DATE	: 07 Feb 2024	
CO-INVESTIGATOR	: Zafri Azran Abdul Majid Mohd Izzuddin Mohd Tamrin	
STUDY SITE	: Kulliyah of Allied Health Sciences, IIUM	
SAMPLE SIZE	: 50	
ETHICAL EXPIRY DATE	: 26 March 2025	
The IIUM Research Ethics Committee (IREC) operates in accordance to the Dedaration of Helsinki, International Conference of Harmonization Good Clinical Practice Guidelines (ICH-GCP), Malaysia Good Clinical Practice Guidelines and Council for International Organizations of Medical Sciences (COMS) International Ethical Guidelines		
The following documents have been received and reviewed to the above study:—		
- Study Proposal/Protocol: Version 1, dated 19 Dec 2023 - Approval Letter from Kulliyah of Allied Health Sciences, IIUM - Principal Investigator's CV		
Decision by IIUM Research Ethics Committee (IREC):		
(✓) Approved		
() Disapproved		
Date of Approval: 26 March 2024		

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