POZNAN UNIVERSITY OF TECHNOLOGY

Faculty of Computing and Telecommunication

Doctor of Philosophy Dissertation

LEVERAGING ARTIFICIAL INTELLIGENCE IN THE AREA OF CONNECTOMICS FOR AUTOMATED EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE

Anna Lisowska

Supervisor: Paweł Śniatała
Secondary supervisor: Joanna Weissenberg

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Summary

Introduction

The aging global population, combined with the growing complexity of health problems, is placing unprecedented pressure on hospital-centric healthcare systems. This strain is exacerbated by the reactive nature of traditional healthcare, which often addresses diseases only after they have manifested, rather than preventing or diagnosing them at an earlier stage. As the population ages, neurodegenerative diseases like Alzheimer's Disease (AD) are becoming more prevalent, creating an urgent need for early diagnosis and intervention.

Recent advancements in healthcare, particularly the digitalisation of medical records, have opened new avenues for data analysis, leading to more evidence-based approaches to diagnosis and patient care. Artificial Intelligence (AI) has emerged as a powerful tool in this context, offering the potential to support clinicians in delivering personalised, preventative care. However, several challenges must be addressed before AI can be widely adopted in clinical practice. These challenges include the need for improved diagnostic performance, the ability to work with small, complex datasets typically available in clinical settings, and the necessity of producing diagnostic decisions that are both understandable to humans and capable of providing new insights into disease mechanisms.

The primary goal of this thesis was to develop a machine learning solution that could automate the early diagnosis of dementia, particularly Alzheimer's Disease, and could one day be realistically applied in clinical practice. To achieve this, we set out to satisfy the following criteria:

- Achieve improved diagnostic performance compared to state-of-the-art solutions.
- Work on small, highly complex data that can be realistically obtained in clinics.
- Spot anomalies before the onset of serious symptoms.
- Integrate complementary information from a variety of sources.
- Produce diagnostic decisions that are understandable to clinicians.
- Derive new insights into the mechanisms of Alzheimer's Disease.

Innovative Approach: Morphological Brain Network

Recognising the limitations of traditional diagnostic methods, we decided to focus on brain morphology—the structural characteristics of the brain that can provide early indicators of neurodegenerative diseases. We introduced a novel form of connectomic brain data called the Morphological Brain Network. This network captures subtle morphological changes in the brain that are often the first indicators of Alzheimer's Disease. By focusing on these structural changes, rather than

solely on functional or metabolic alterations, we aimed to create a more sensitive diagnostic tool capable of detecting the earliest stages of the disease.

The Morphological Brain Network was designed to serve as an input to our diagnostic pipeline, allowing us to avoid the costly and often noisy screening procedures typically associated with neuroimaging. To further enhance the diagnostic power of our approach, we developed a new data structure called the Brain Multiplex. This structure integrates multiple morphological views of the brain into a multi-layer network, each layer representing a different aspect of brain morphology, such as cortical thickness, gyrification, or sulcal depth. By combining these views, we were able to obtain a more comprehensive picture of the brain's structural changes, improving the accuracy of our diagnostic model.

Machine Learning Pipeline and Methodology

To bring data from different modalities together, we introduced a machine learning pipeline that combines feature fusion methods from two distinct families: correlational methods and discriminative methods. This ensemble model was designed to maximise the relevant information extracted from the data while minimising noise, making the best use of the limited data that would be available in clinical settings.

Morphological Brain Network Construction: We began by constructing the Morphological Brain Network from high-resolution MRI scans. This process involved segmenting the brain into various regions of interest (ROIs) and analysing morphological properties such as cortical thickness, surface area, and curvature. These properties were then used to create a network where nodes represent brain regions and edges represent the morphological similarity between these regions.

Brain Multiplex Structure: The Brain Multiplex structure allowed us to integrate multiple morphological perspectives into a cohesive diagnostic model. Each layer of the multiplex corresponds to a different morphological feature, and the interactions between these layers provided additional insights into the structural changes associated with Alzheimer's Disease.

Feature Fusion and Ensemble Learning: Given the complexity and high dimensionality of the data, we employed feature fusion techniques to combine information from the different layers of the Brain Multiplex. Correlational methods like Canonical Correlation Analysis (CCA) and discriminative methods like Linear Discriminant Analysis (LDA) were used to extract the most informative features. These features were then fed into an ensemble learning model, which combined the predictions from multiple classifiers to produce a final diagnosis.

Validation and Testing: We validated our framework using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) GO public database. This dataset includes MRI scans from patients with early mild cognitive impairment (eMCI), a condition often considered a precursor to Alzheimer's Disease, as well as healthy controls. Our model's performance was evaluated based on its ability to distinguish between eMCI patients and healthy controls, as well as its sensitivity to subtle morphological changes in the brain.

Results

Our experiments demonstrated the effectiveness of the proposed approach in diagnosing Alzheimer's Disease at its earliest stages, significantly outperforming existing state-of-the-art methods.

Key Findings:

- **Enhanced Sensitivity:** The Morphological Brain Network was highly sensitive to small changes in brain morphology, which are often the earliest indicators of Alzheimer's Disease. By capturing these subtle changes, our model was able to detect the disease at a stage when traditional methods might miss it.

- **Superior Diagnostic Performance:** The ensemble learning approach, which combined both correlational and discriminative feature fusion methods, achieved higher diagnostic accuracy compared to existing models. This demonstrates the effectiveness of our methodology in handling complex, high-dimensional brain data.

- **Novel Biomarkers:** In addition to improving diagnostic accuracy, our model identified novel biomarkers of early Alzheimer's Disease. These biomarkers, derived from the morphological properties of specific brain regions, offer new insights into the disease's progression and may guide future research in the field.

- **Robustness and Generalisability:** Our model's robustness was tested across different subsets of the data, showing consistent performance, which suggests that it could be generalizable to other populations and clinical settings. This is a critical consideration for any diagnostic tool intended for widespread clinical application.

Discussion

The results of our research highlight the potential of the Morphological Brain Network and the associated machine learning pipeline to transform the early diagnosis of Alzheimer's Disease. By focusing on brain morphology, we were able to develop a more sensitive and specific diagnostic tool that could detect Alzheimer's Disease at an earlier stage than traditional methods. Our research also contributes to the field of connectomics by introducing the Brain Multiplex structure, which integrates multiple morphological views into a cohesive diagnostic framework. This multi-layer approach not only improves diagnostic accuracy but also provides new insights into the structural changes that occur in the brain during the early stages of Alzheimer's Disease. One of the significant contributions of our work is the identification of novel biomarkers for early Alzheimer's Disease. These biomarkers, which are derived from the morphological properties of specific brain regions, could serve as the basis for new diagnostic and therapeutic strategies. However, while our results are promising, there are limitations to our study that must be addressed in future work.

Limitations and Future Research:

- **Dataset Size and Diversity:** One of the primary limitations of our study is the relatively small size and lack of diversity in the dataset used for validation. Future research should focus on expanding the dataset to include a more diverse population, which would help to further validate the generalizability of our model.

- **Integration of Additional Data:** While our model focused on brain morphology, integrating other types of data, such as functional connectivity or metabolic changes, could provide a more comprehensive understanding of Alzheimer's Disease and improve diagnostic accuracy.

- **Longitudinal Studies:** Future research should also consider longitudinal studies to track the progression of Alzheimer's Disease over time, which would allow for the validation of our model's predictive capabilities.

Conclusion

In conclusion, this thesis presents a novel approach to the early diagnosis of Alzheimer's Disease by leveraging advancements in artificial intelligence and connectomics. We introduced the Morphological Brain Network and the Brain Multiplex structure, which together provide a powerful framework for analysing brain morphology and detecting subtle changes associated with Alzheimer's Disease.

Our findings demonstrate that this approach significantly improves diagnostic accuracy and sensitivity compared to existing methods, making it a promising tool for early diagnosis in clinical settings. Additionally, our research has identified novel biomarkers of early Alzheimer's Disease, which could guide future research and therapeutic development.

As the global population continues to age, the need for effective diagnostic tools for neurodegenerative diseases will only increase. We believe that the Morphological Brain Network and the associated machine learning pipeline represent a significant step forward in this area, offering a new approach to understanding and diagnosing Alzheimer's Disease at its earliest stages.

This work not only advances the field of AI in healthcare but also provides practical solutions that could one day be integrated into clinical practice, improving patient outcomes and contributing to our understanding of neurodegenerative diseases.

Streszczenie

Wprowadzenie

Starzejąca się globalna populacja, w połączeniu z rosnącą złożonością problemów zdrowotnych, wywiera bezprecedensową presję na systemy opieki zdrowotnej oparte na szpitalach. Ten ciężar jest pogłębiany przez reaktywny charakter tradycyjnej opieki zdrowotnej, która często zajmuje się chorobami dopiero po ich ujawnieniu, zamiast zapobiegać im lub diagnozować je na wcześniejszym etapie. W miarę starzenia się populacji, choroby neurodegeneracyjne, takie jak choroba Alzheimera (AD), stają się coraz bardziej powszechne, co stwarza pilną potrzebę wczesnej diagnozy i interwencji.

Najnowsze osiągnięcia w dziedzinie opieki zdrowotnej, zwłaszcza cyfryzacja dokumentacji medycznej, otworzyły nowe możliwości analizy danych, prowadząc do bardziej opartego na dowodach podejścia do diagnostyki i opieki nad pacjentem. Sztuczna inteligencja (AI) pojawiła się jako potężne narzędzie w tym kontekście, oferując potencjał wspierania lekarzy w dostarczaniu spersonalizowanej, prewencyjnej opieki. Niemniej jednak, przed szerokim zastosowaniem AI w praktyce klinicznej należy rozwiązać szereg wyzwań. Wyzwania te obejmują potrzebę poprawy dokładności diagnostycznej, zdolność do pracy z małymi, złożonymi zestawami danych, które są zazwyczaj dostępne w klinikach, oraz konieczność wydawania decyzji diagnostycznych, które są zrozumiałe dla ludzi i mogą dostarczyć nowych wglądów w mechanizmy chorób.

Głównym celem tej pracy doktorskiej było opracowanie rozwiązania opartego na uczeniu maszynowym, które mogłoby zautomatyzować wczesną diagnozę demencji, w szczególności choroby Alzheimera, i być realistycznie stosowane w praktyce klinicznej. Aby to osiągnąć, postawiliśmy sobie za cel spełnienie następujących kryteriów:

- Osiągnięcie lepszej dokładności diagnostycznej w porównaniu z nowoczesnymi rozwiązaniami.
- Praca na małych, wysoce złożonych danych, które można realistycznie uzyskać w klinikach.
- Wykrywanie anomalii przed pojawieniem się poważnych objawów.
- Integracja komplementarnych informacji z różnych źródeł.
- Wydawanie decyzji diagnostycznych, które są zrozumiałe dla lekarzy.
- Pozyskiwanie nowych wglądów w mechanizmy choroby Alzheimera.

Innowacyjne Podejście: Morfologiczna Sieć Mózgu

Zdajemy sobie sprawę z ograniczeń tradycyjnych metod diagnostycznych i postanowiliśmy skupić się na morfologii mózgu — cechach strukturalnych mózgu, które mogą dostarczać wczesnych wskaźników chorób neurodegeneracyjnych. Wprowadziliśmy nową formę danych konnektomicznych mózgu, nazwaną Morfologiczną Siecią Mózgu. Sieć ta rejestruje subtelne zmiany morfologiczne w

mózgu, które często są pierwszymi wskaźnikami choroby Alzheimera. Skupiając się na tych zmianach strukturalnych, a nie tylko na funkcjonalnych lub metabolicznych, staraliśmy się stworzyć bardziej czułe narzędzie diagnostyczne, zdolne do wykrywania najwcześniejszych stadiów choroby.

Morfologiczna Sieć Mózgu została zaprojektowana jako wkład do naszego algorytmu diagnostycznego, co pozwala nam unikać kosztownych i trudnych do zrealizowania procedur przesiewowych, które zazwyczaj wiążą się z neuroobrazowaniem. Aby dodatkowo zwiększyć moc diagnostyczną naszego podejścia, opracowaliśmy nową strukturę danych nazwaną Brain Multiplex. Struktura ta integruje wiele morfologicznych widoków mózgu w sieć wielowarstwową, z każdą warstwą reprezentującą inny aspekt morfologii mózgu, taki jak grubość kory, gyrifikacja lub głębokość bruzd. Dzięki połączeniu tych widoków uzyskaliśmy bardziej kompleksowy obraz zmian strukturalnych w mózgu, poprawiając dokładność naszego modelu diagnostycznego.

Algorytm Uczenia Maszynowego i Metodologia

Aby połączyć dane z różnych modalności, wprowadziliśmy algorytm uczenia maszynowego, który łączy metody fuzji cech z dwóch odrębnych rodzin: metod korelacyjnych i dyskryminacyjnych. Ten model zespołowy został zaprojektowany w celu maksymalizacji istotnych informacji wydobytych z danych przy jednoczesnym minimalizowaniu szumu, co umożliwia najlepsze wykorzystanie ograniczonych danych dostępnych w warunkach klinicznych.

Budowa Morfologicznej Sieci Mózgu: Zaczęliśmy od budowy Morfologicznej Sieci Mózgu na podstawie skanów MRI o wysokiej rozdzielczości. Proces ten polegał na segmentacji mózgu na różne regiony zainteresowania (ROI) i analizie cech morfologicznych, takich jak grubość kory, powierzchnia i krzywizna. Następnie wykorzystaliśmy te cechy do stworzenia sieci, w której węzły reprezentują regiony mózgu, a krawędzie reprezentują morfologiczne podobieństwo między tymi regionami.

Struktura Brain Multiplex: Struktura Brain Multiplex umożliwiła nam integrację wielu morfologicznych perspektyw w spójnym modelu diagnostycznym. Każda warstwa tego multiplexu odpowiada innej cesze morfologicznej, a interakcje między tymi warstwami dostarczały dodatkowych wglądów w zmiany strukturalne związane z chorobą Alzheimera.

Fuzja Cech i Uczenie Zespołowe: Biorąc pod uwagę złożoność i wysoką wymiarowość danych, zastosowaliśmy techniki fuzji cech, aby połączyć informacje z różnych warstw Brain Multiplex. Metody korelacyjne, takie jak kanoniczna analiza korelacyjna (CCA) i metody dyskryminacyjne, takie jak analiza dyskryminacyjna (LDA), zostały użyte do wydobycia najbardziej informatywnych cech. Te cechy zostały następnie podane do modelu uczenia zespołowego, który łączył przewidywania z wielu klasyfikatorów w celu uzyskania ostatecznej diagnozy.

Walidacja i Testowanie: Nasz algorytm został zwalidowany za pomocą danych z publicznej bazy danych Alzheimer's Disease Neuroimaging Initiative (ADNI) GO. Zbiór danych obejmuje skany MRI pacjentów z wczesnym łagodnym upośledzeniem poznawczym (eMCI), stanem często uważanym za prekursor choroby Alzheimera, oraz zdrowych osób kontrolnych. Wydajność naszego modelu była oceniana pod kątem jego zdolności do rozróżniania pacjentów z eMCI i zdrowych osób kontrolnych oraz jego czułości na subtelne zmiany morfologiczne w mózgu.

Wyniki

Nasze eksperymenty wykazały skuteczność proponowanego podejścia w diagnozowaniu choroby Alzheimera we wczesnych stadiach, znacznie przewyższając istniejące nowoczesne metody.

Kluczowe Ustalenia:

- **Zwiększona Czułość:** Morfologiczna Sieć Mózgu okazała się wysoce czuła na małe zmiany morfologiczne w mózgu, które często są najwcześniejszymi wskaźnikami choroby Alzheimera. Dzięki rejestrowaniu tych subtelnych zmian, nasz model był w stanie wykryć chorobę na etapie, na którym tradycyjne metody mogłyby ją przeoczyć.
- **Lepsza Wydajność Diagnostyczna:** Nasze podejście uczenia zespołowego, które łączyło zarówno metody fuzji cech korelacyjnych, jak i dyskryminacyjnych, osiągnęło wyższą dokładność diagnostyczną w porównaniu do istniejących modeli. To pokazuje skuteczność naszej metodologii w radzeniu sobie z złożonymi, wysokowymiarowymi danymi mózgowymi.
- **Nowe Biomarkery:** Oprócz poprawy dokładności diagnostycznej, nasz model zidentyfikował nowe biomarkery wczesnej choroby Alzheimera. Biomarkery te, pochodzące z cech morfologicznych określonych regionów mózgu, oferują nowe wglądy w postęp choroby i mogą kierować przyszłymi badaniami w tej dziedzinie.
- **Solidność i Uogólnialność:** Solidność naszego modelu została przetestowana na różnych podzbiorach danych, pokazując spójne wyniki, co sugeruje, że może być on uogólnialny na inne populacje i środowiska kliniczne. Jest to krytyczny aspekt dla każdego narzędzia diagnostycznego przeznaczonego do szerokiego zastosowania klinicznego.

Dyskusja

Wyniki naszych badań podkreślają potencjał Morfologicznej Sieci Mózgu i związanego z nią algorytmu uczenia maszynowego do transformacji wczesnej diagnozy choroby Alzheimera. Skupiając się na morfologii mózgu, byliśmy w stanie opracować bardziej czułe i specyficzne narzędzie diagnostyczne, które mogłoby wykryć chorobę Alzheimera na wcześniejszym etapie niż tradycyjne metody. Nasze badania wnoszą również wkład w dziedzinę konnektomiki, wprowadzając strukturę Brain Multiplex, która integruje wiele morfologicznych widoków w spójne ramy diagnostyczne. To wielowarstwowe podejście nie tylko poprawia dokładność diagnostyczną, ale także dostarcza nowych wglądów w zmiany strukturalne zachodzące w mózgu podczas wczesnych stadiów choroby Alzheimera.

Jednym z najważniejszych wkładów naszej pracy jest identyfikacja nowych biomarkerów wczesnej choroby Alzheimera. Biomarkery te, pochodzące z morfologicznych właściwości określonych regionów mózgu, mogą stanowić podstawę dla nowych strategii diagnostycznych i terapeutycznych. Jednakże, mimo że nasze wyniki są obiecujące, istnieją ograniczenia, które muszą zostać uwzględnione w przyszłych badaniach.

Ograniczenia i Przyszłe Badania:

- **Rozmiar i Różnorodność Zbioru Danych:** Jednym z głównych ograniczeń naszego badania jest stosunkowo mały rozmiar i brak różnorodności w zbiorze danych użytym do walidacji. Przyszłe badania powinny skupić się na rozszerzeniu zbioru danych, aby uwzględnić bardziej zróżnicowaną populację, co pomoże w dalszej walidacji uogólnialności naszego modelu.
- **Integracja Dodatkowych Danych:** Chociaż nasz model skupił się na morfologii mózgu, integracja innych typów danych, takich jak łączność funkcjonalna lub zmiany metaboliczne, mogłaby dostarczyć bardziej kompleksowego zrozumienia choroby Alzheimera i poprawić dokładność diagnostyczną.

- **Badania Podłużne:** Przyszłe badania powinny również uwzględniać badania podłużne, aby śledzić postęp choroby Alzheimera w czasie, co pozwoliłoby na walidację predykcyjnych możliwości naszego modelu.

Wnioski

Podsumowując, niniejsza praca przedstawia nowatorskie podejście do wczesnej diagnozy choroby Alzheimera, wykorzystując zaawansowania w sztucznej inteligencji i konnektomice. Wprowadziliśmy Morfologiczną Sieć Mózgu i strukturę Brain Multiplex, które razem tworzą potężne ramy do analizy morfologii mózgu i wykrywania subtelnych zmian związanych z chorobą Alzheimera.

Nasze ustalenia pokazują, że to podejście znacznie poprawia dokładność i czułość diagnostyczną w porównaniu do istniejących metod, co czyni go obiecującym narzędziem do wczesnej diagnozy w warunkach klinicznych. Dodatkowo, nasze badania zidentyfikowały nowe biomarkery wczesnej choroby Alzheimera, które mogą kierować przyszłymi badaniami i rozwojem terapeutycznym.

W miarę jak globalna populacja nadal się starzeje, potrzeba skutecznych narzędzi diagnostycznych dla chorób neurodegeneracyjnych będzie tylko rosła. Wierzymy, że Morfologiczna Sieć Mózgu i związany z nią algorytm uczenia maszynowego stanowią znaczący krok naprzód w tej dziedzinie, oferując nowe podejście do zrozumienia i diagnozowania choroby Alzheimera na jej najwcześniejszych etapach.

Nasza praca nie tylko rozwija dziedzinę AI w opiece zdrowotnej, ale także dostarcza praktycznych rozwiązań, które mogą w przyszłości zostać zintegrowane z praktyką kliniczną, poprawiając wyniki leczenia pacjentów i przyczyniając się do lepszego zrozumienia chorób neurodegeneracyjnych.

Abstract

The aging World population and the growing complexity of health problems it experiences puts increasing pressure on the hospital-centric healthcare system. Recent developments in healthcare, with digitalisation of the medical records opening new possibilities for data analysis leading to a more evidence-based approach to diagnosis and patient care. AI implementation in healthcare to support clinicians in delivering preventative personalised patient care is underway, but several challenges still need to be addressed before it can become a widely adopted technology. The purpose of this project was to develop a machine learning solution that would deliver an automated diagnosis, focusing on early dementia, and could be realistically applied in clinical practice by satisfying the following criteria:

- Achieve improved diagnostic performance comparing to the state-of-the-art solutions,
- Work on small highly complex data that can be realistically obtained in clinics,
- Be able to spot anomalies before the onset of serious symptoms,
- Bring complementary information together from a variety of sources,
- Produce diagnostic decision understandable by a human,
- Derive new insight into the mechanism of the disease.

To do that, we first introduced a new form of connectomic brain data called Morphological Brain Network that could be used as an input to a diagnostic pipeline while avoiding costly screening of patients. We also proposed a new data structure called Brain Multiplex that brings further important information into the system, which could be valuable in making a correct diagnosis and contribute to a better understanding of the disease progression. To bring data from different modalities together, we introduced our proposed machine learning pipeline that combines feature fusion methods from two different families: correlational methods and discriminative methods into one ensemble model. This way, we were able to design a model capable of combining data from multiple sources in a way that maximises the relevant information and minimises the noise to make the best use of the limited data available. We tested our framework on data from patients with early mild cognitive impairment and healthy controls to evaluate our framework's capacity to diagnose Alzheimer's Disease at the very early stages. We demonstrate that our system is sensitive to small changes in patients' brain morphology and outperforms the state-of-the-art solutions on the ADNI GO dataset. We were also able to derive new insights into the mechanism of Alzheimer's Disease progression across the brain at its early stages by identifying brain connections most affected by early dementia in both hemispheres. Finally, we made recommendations for the directions of future research to further improve upon our proposed framework and contribute to our understanding of early dementia progression in the brain.

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Chapter 1

Challenges in modern healthcare

1.1 Healthcare Status Quo

1.1.1 The aging population

A drastic demographic move is extending across the World, especially affecting developed countries. We are seeing a shift in the average age of the global population, which is getting older, mostly because of increasing life expectancy and a declining birth rate [3]. An aging population typically means a declining workforce and an increase of people retired from the job market. This can put pressure on the industries in which the demand for services exceeds the supply of the workforce providing these services. One of the most affected industries with a huge impact Worldwide is healthcare. It is modern healthcare combined with recent developments in science that drove the increase in life expectancy and decline in birth rates, both of which are major achievements with significant implications for future generations. In 2020 people of 60 years of age and over accounted for 13.7% of the global population (see fig.1.1) [1]. Since elderly citizens have a widespread positive impact on the local communities, such as actively volunteering and decreasing the crime rates, they should be considered a valuable asset in any society [4]. Unfortunately, the same age group tends to have accumulated more health conditions over life and consequently be affected by long-term illness more than young people. Indeed, elderly people account for around 70% of healthcare professionals' work hours in the United States and the United Kingdom [5]. Moreover, the longer people live, the more likely they are to develop multiple comorbidities (different diseases coexisting in a single person). This results in a more challenging patient diagnosis and treatment. So, aging population means not only a rise in demand for healthcare and social care but also rising demand for more complex care and holistic approach to patients' treatment [6].

Age Group (years)	Number of People in 2020	Percentage of Global Population
20 and below	2.6 billion	33.2%
20 - 39	2.3 billion	29.9%
40 - 59	1.8 billion	23.1%
60 - 79	918 million	11.8%
80 - 99	147 million	1.9%
100 and above	0.6 million	0.01%

FIGURE 1.1: *World population by age group in 2020.* Figure adapted from [1]

1.1.2 Hospital-centric system

The problem with the current healthcare system is that it is not adjusted to the treatment of long-term complex illnesses that are prevalent in the elderly population. The highly centralised hospital-centric system is best suited to treat people following accidents or patients with short-term health issues that are relatively straightforward to diagnose and treat on an ad-hoc basis. The system is reactive in its nature, meaning it focuses on treating people who are already ill, but has limited capacity to help people stay healthy and consequently limit the demand for hospital-based treatment. This further contributes to the burden exerted on healthcare systems from people who could avoid having the need to be seen by a doctor by applying preventative measures, such as changing lifestyle or getting community-based advice, and from people who received treatment before but did not stay healthy enough to avoid readmission to the hospital. Indeed, it is estimated that one in ten patients of the National Health Service (NHS) in the UK suffers some form of avoidable harm in hospital because early warning signs about a deterioration in their condition are not picked up on in time [7–9]. In addition to delayed diagnosis, the patients often experience delays in admission to the hospital, delays of progression through the emergency department, delays in getting treatment from a specialist, and delays in the discharge of patients to social and post-hospital care. Furthermore, according to [10] up to four hundred thousand people die each year from preventable medical errors at the hands of the US healthcare system, making it the third leading cause of death in America. This is a result of several factors that make the current state of healthcare unsustainable:

- First of all, healthcare is already experiencing significant shortages of resources. With the aging population and the continuous emergence of complex diseases, there are rising shortages of qualified healthcare staff to match the demand. So far, the NHS tried to offset that shift by extending the work hours of the existing workforce [11], but long working hours lead to overworked staff, professional burnout, and preventable mistakes in decision-making and patient treatment. Together with rising healthcare costs and increasing medicine prices, delivery of care becomes more and more unsustainable, and delivery of good quality care is an ever further goal. Even today, across the NHS, patients receive different standards of care depending on the availability of trained medical staff at local health services, with variations in care pathways common, exacerbated by varying access to social and community care locally [12].

- Secondly, the introduction of the fee-for-service model led to inefficient care delivery. Currently, the healthcare business model is not based on outcomes, but rather on fee for service [13]. This means the hospital is not rewarded for the positive outcomes of their patients but based on the procedures (i.e. surgeries) it delivered. By devaluating the interaction time between doctors and patients and putting more value (monetary) on procedures rather than people's outcomes, the healthcare system loses patients' trust. The deterioration of the patient-doctor relationship has a further negative impact on the effectiveness of patient treatment, with patients being less likely to follow doctor's recommendations and stick to the treatment regime and on the doctors' work satisfaction contributing to early professional burnout [14].

- Thirdly, the lack of resources for the personal treatment of patients is further exacerbated by personal responses to treatment. Nowadays, the diagnosis and treatment recommendations are primarily based on statistics, rather than individual patient's needs. The way medicine evolved is that it treats everybody the same (in terms of the screening test they need, the food

they should eat, and take this kind of medicine in case they have a certain diagnosis), but not all patients respond in a similar manner to the same treatment. Indeed, some medicines may be safe to use and help the condition of most people but at the same time be detrimental to the health of others who are affected by the same disease, with typically prescribed medicine working in a minority of people [15]. Most often, the disease is diagnosed based on the range of symptoms experienced by the individual, but the underlying cause of the symptoms may be different across patients, especially when the interplay of many illnesses and medicines taken is considered. With recent developments in science and technology, there are many more treatment options available now than 20 years ago, adding to the complexity of a patient's journey within the healthcare setting [9, 16]. With the advent of deep phenotyping we start realising that we are incredibly unique (i.e. even identical twins can have markedly different responses in terms of blood glucose, triglyceride, and insulin level following ingestion of the same food) [17]. Without taking this individual complexity into account and applying a one-size-fits-all strategy, the medical intervention can result in a waste of resources and avoidable harm caused to the patient. However, the information and procedures we have been using so far may not be enough to support personalised medicine approach to patients.

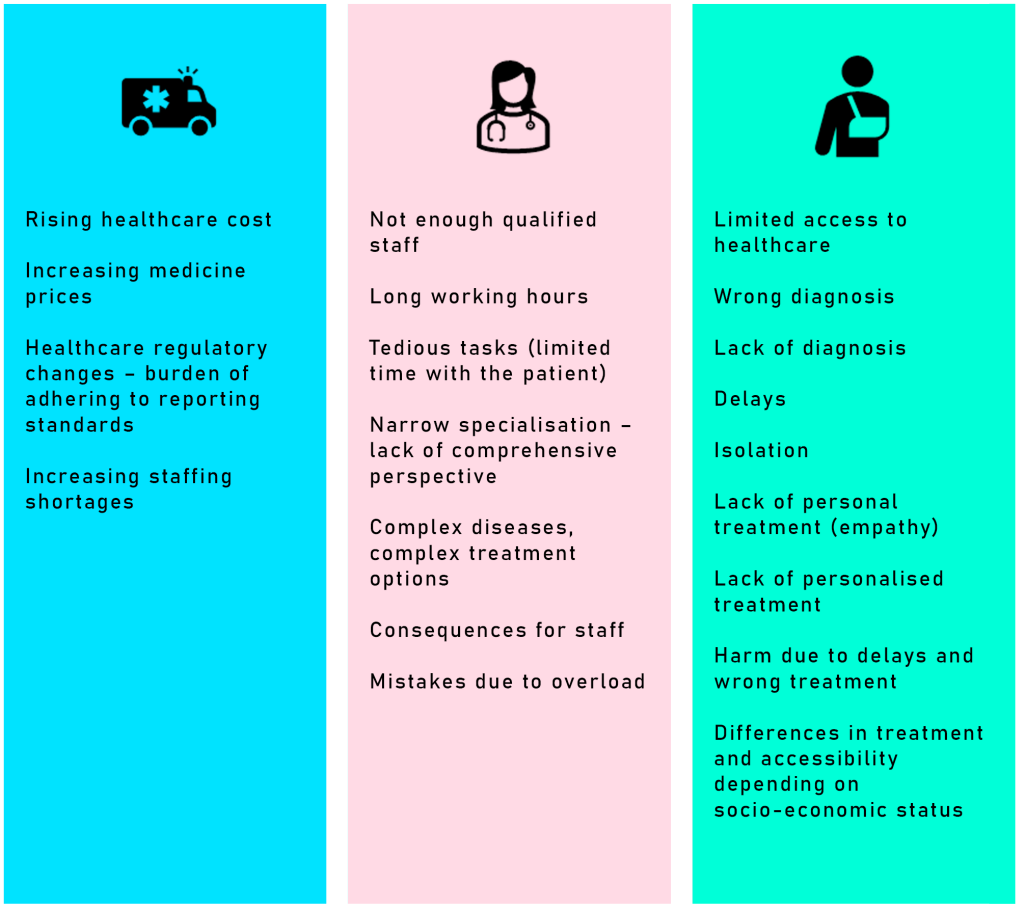


FIGURE 1.2: *Current issues faced by the healthcare system, medical staff, and patients.*

1.2 Recent developments towards a value-based future

Things are slowly changing in healthcare. In the United States following the great recession in 2009, the American Recovery & Reinvestment Act pushed the adoption of electronic medical health records (EHR) by rewarding each clinician who adopted the EHR in their practice with $\$17k$ and taking $\$4k$ from each clinician who did not adopt the EHR within 4 years from the rollout of the reform [18]. This resulted in 95% of clinical settings in the United States employing EHR in their daily practice, proving that with the right incentive drastic change can happen within a short period of time [19]. Right about the same time, the same administration introduced a payment reform heading towards "value-based care" to align the monetary reimbursement with patients' outcomes [20]. In this model, the quality and the efficiency of healthcare provided become a part of the formula that dictates how much the healthcare provider will get paid per patient treated, providing a whole new incentive for a better quality of care. Similarly, NHS in the United Kingdom, just like most health systems in the World, lags behind other industries when it comes to the use of digital technologies, even though digital technology was already present for 20 years. The advent of the Covid-19 pandemic provided the incentive that was necessary to start employing digital technology in practice across NHS. Now, patients in the UK are able to connect with their general practitioners through "NHS Near Me" to receive an online appointment, get an electronic medicine prescription, or referral to a specialist [21]. Clinicians are also able to monitor the blood pressure of patients with heart conditions and conduct routine monitoring of patients with chronic obstructive pulmonary disease (COPD) completely remotely [22, 23].

1.2.1 Digitalisation and current use of data

With the recent progress in healthcare digitalisation and the application of EHR in clinical practice, more and more patient data is collected and available for analysis. Having the incentive to head towards value-based care, i.e. providing quality service at a lower cost, it becomes essential to derive insight from the data collected within the healthcare setting. Two main methods of learning from clinical data are applied in practice today:

- Reporting – designed and used to provide a summarising view of what happened in the past. Commonly used to look at claims data to answer questions like how many beds we occupied in a hospital in a given time period, how many pills were prescribed, or how many patients received certain kinds of treatment.
- Risk scores – used by clinicians to attempt answering questions relating to the likelihood of events happening in the future, such as: How many diabetics are they likely to see? Who these diabetics exactly are likely to be? One way these are predicted is by using clinical intuition to map the limited structured data about the patients available in the hospital database. Another way is to use traditional statistical logistic regression-based methods.

1.2.2 Risk scores

There are different products that calculate risk scores in a clinical setting (i.e. LACE, John Hopkins) [24, 25]. Working with claims data from one or more institutions, they are attempting to say in advance that there is probably a certain number of factors, also known as features (i.e. 5 factors or 12 factors), that are important in making the prediction. Then, they change each one of these items a little bit and observe if that affects the underlying characteristic of the studied population, and validate it mathematically (look if this slight change affects the statistical

significance of the model). To apply the calculated risk score to many other organisations as widely as possible, they turn the model into a set of rules by assigning points to each factor, with more points assigned to the factors that, when changed, resulted in a bigger change in the population characteristics (for example, for readmission of the patient into the hospital within six months following a procedure contributes 3 points into the final risk score).

1.2.3 Risk scores – limitations

While risk scores can be useful for making simple assumptions about the future based on previous trends, several considerations need to be taken into account when applying risk scores in a clinical setting.

- Risk scores consider relatively few data points when making a prediction. They mainly rely on previously defined factors, such as claims data and disease codes (ICD-10) which are often inaccurate. Studies conducted across 6 academic medical centers found that even 80% of people with colorectal cancer codes didn't have cancer. All of them underwent a colonoscopy procedure, but only 20% of them actually had cancer [26, 27]. Another study showed that these numbers can be about 50% inaccurate in case of heart failure [28].

- Risk score-based methods ignore the content of clinical notes, also known as, free text data, which is the main way clinicians communicate with one another to relay important information about patients and procedures [29].

- Risk scores are often one-size-fits-all. They apply the same formula to all diseases and all populations. Applying one scoring system to an entire population to understand risk is a less granular solution than what the patient population requires [30]. For example, clinicians would not apply the same way of thinking when trying to understand risk in a patient with a complicated pregnancy as in a geriatric patient on end-of-life care.

- Risk score-based methods are static, while the patient population and the interventions delivered are dynamic in nature. A study analysing a population of "superutilisers" (patients consuming a majority of clinical resources) found that 50% of the original cohort got better, left the study, or died within the first 7 months and within 2 years only 14% of the population was still a part of the study with new patients replacing the majority of the original cohort [31]. Since, if we build a model that understands the state of things today and it will become outdated in just a few months, we need a solution that can consider continuous personal data rather than a specific hospital cohort and that continuously evolves as it is presented with new incoming data.

- The kind of questions that risk scores help answer are reactive. Doctors already know who is sick as they are already seeing these patients anyway. They want to know who is actionable, who is most likely to end up in the emergency department soonest, and perhaps most importantly, who is heading towards a disease that can be prevented from happening. Doctors need to be able to answer these kinds of questions in order to provide preventative care, but these cannot be answered by the one-size-fits-all risk model [32].

1.2.4 The problems of data in healthcare

There are significant challenges connected to healthcare data that limit its potential use in making risk predictions. Unlike in other industries, which use data (i.e. sales data on how many items

were sold, how many clients served, revenue made, etc.) mainly to optimise spending money as effectively as possible (such as supermarkets, casinos, and even waste management), healthcare has limited quantitative or reliable data. This is largely due to the way the EHR are being adopted in practice. EHR platform providers did not design the software for value-based care, but to fit in with the fee-for-service model with the following goals:

- Collect claims data to capture units of service delivered that the healthcare provider can get paid for.
- Save clinical notes that medical staff use to inform one another about what happened during their shifts. Over 50% of EHR data is in the form of free text, unstructured data that cannot be used in making predictions by the risk-score based techniques [29].
- Keeping legal documentation to protect the medical staff and the institution from legal prosecution in case their actions are incorrect, which adds a layer of ambiguity to the data present in the system.

Clearly, from adopting the EHR there are important things missing, such as learning from the data with the aim of service improvement. This is further exacerbated by the lack of one agreed-upon set of guidelines when it comes to the introduction of value-based care nationally. Healthcare is currently experiencing a continuous state of payment reforms, which means that the same care provider treating the same patients could be eligible for several different methods of reimbursement depending on who is responsible for paying the bill [20, 33]. Each of these would have its own reporting requirement adding more workload to the medical staff and more data that is not designed for analytics, leaving healthcare with data that is harder to utilise than the data in other fields. However, if we could make use of healthcare data to its best potential, the return on the investment would be greater than in any other industry, since in health it can make the biggest difference to people's lives.

Chapter 2

Machine Learning in Healthcare

As a result of present developments in healthcare digitalisation and an ongoing implementation of value-based care, the current approaches to healthcare analytics (population health, risk stratification, revenue cycle management, case management, etc.) are dramatically changing [18,20]. What will soon dictate the success of the healthcare provider is no longer limited to statistical analysis of what happened in the past, but the ability to answer questions about what is likely to happen in the future. Questions like: Which patients with frailty are likely to benefit from a home visit? Which patients are likely heading towards diabetes? Which medicine is likely to help the specific patient?

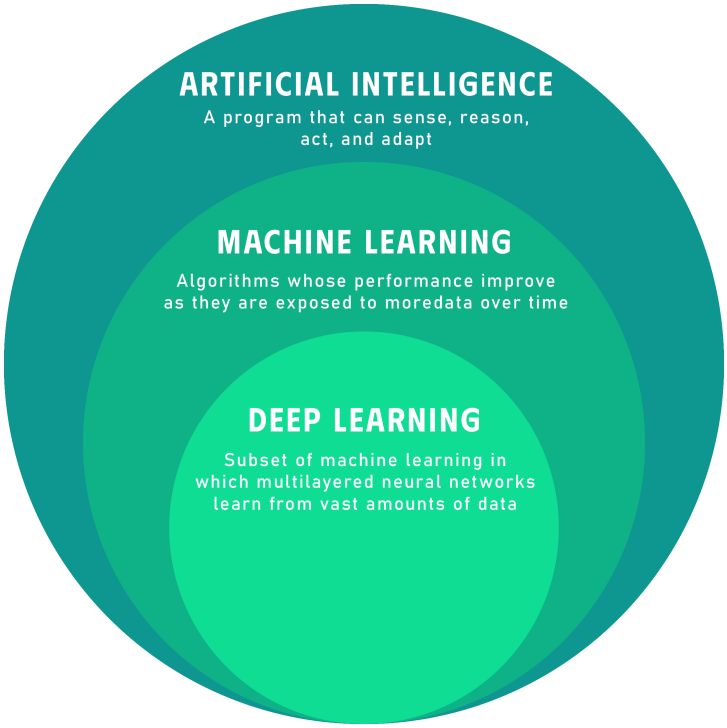


FIGURE 2.1: *The scope of artificial intelligence, machine learning and deep learning*

2.1 Definitions - What is Machine Learning?

Notably, the developments in the growing field of data science and big data technologies provide us with the tools to answer the kinds of questions that could not be answered with the existing approaches. One such technology is machine learning, which is the process by which computer systems can learn directly from data, examples and experience, rather than making predictions solely on the basis of pre-determined rules [34]. The key advantage of machine learning over other statistical methods is the ability to learn by iteratively training analytical models on the data provided. Machine learning is one of the most common forms of Artificial Intelligence (AI) (see fig.2.1) and is already applied across different industries to solve a variety of tasks, such as fraud detection, credit scoring, loan applications, resource optimisation, sentiment analysis, and spam filtering [35–40]. A broader discipline of AI, which refers to any system that can perform "intelligent" tasks, can be divided into two categories. The first category "General AI" is still in its infancy. It encompasses research into whether human intelligence can be augmented or even replicated in a machine [41]. On the other hand, "Narrow AI" involves the application of highly complex, probabilistic algorithms to a narrow range of purposes, for example, recognising signs of disease in a medical scan [42]. This category of AI constitutes the majority of current research into AI technology today with the most promising potential applications across industries, including in healthcare.

2.2 Main applications in medicine: Supervised learning

Currently, the most widely researched application of machine learning in healthcare is precision medicine, which aims to predict the diagnosis and treatment plan that is most likely to succeed for an individual patient based on their unique set of characteristics [9]. So far, the most effective application of machine learning in healthcare involves solving problems whose boundaries can be relatively clearly defined, such as classification problems [43]. For example, identifying whether a patient has a disease or is healthy [Own4], who will respond to a given medication, which grade of cancer is present on a medical scan [Own1], etc. The majority of precision medicine applications rely on supervised learning, which requires a training dataset for which the outcome (i.e. presence of a disease) is known. In general, the classification process begins by defining a cohort of patients and splitting them in half, for example: half of the cohort are patients with hypertension who ended up in the Emergency Department and the other half are patients with hypertension who did not require any emergency treatment. Unlike in the case of risk scores, machine learning does not assume that some predefined factors (such as particular 3 drugs, 4 conditions, or 2 comorbidities) are important in making a prediction about which patient is going to end up in the Emergency Department. Instead, it mathematically learns what it is that makes the patients with hypertension who end up in the Emergency Department different from the patients who do not. To do that, the algorithm can consider all data available for the patient cohort (data from EHR, information about socioeconomic status, any laboratory test results, medical notes, staff communication, and General Practitioner visits) to find what information is correlated to one outcome versus the other. It is, therefore, critical for the model to learn from robust data. Most often in healthcare "Big Data" can mean a small population of patients with "rich data". Once the model is trained and validated, it can be applied to a population, in which we do not have the answer to predict the outcome. The algorithm will be able to return the ordered list of patients with hypertension, who are most likely to be the ones that are going to end up in the Emergency Department.

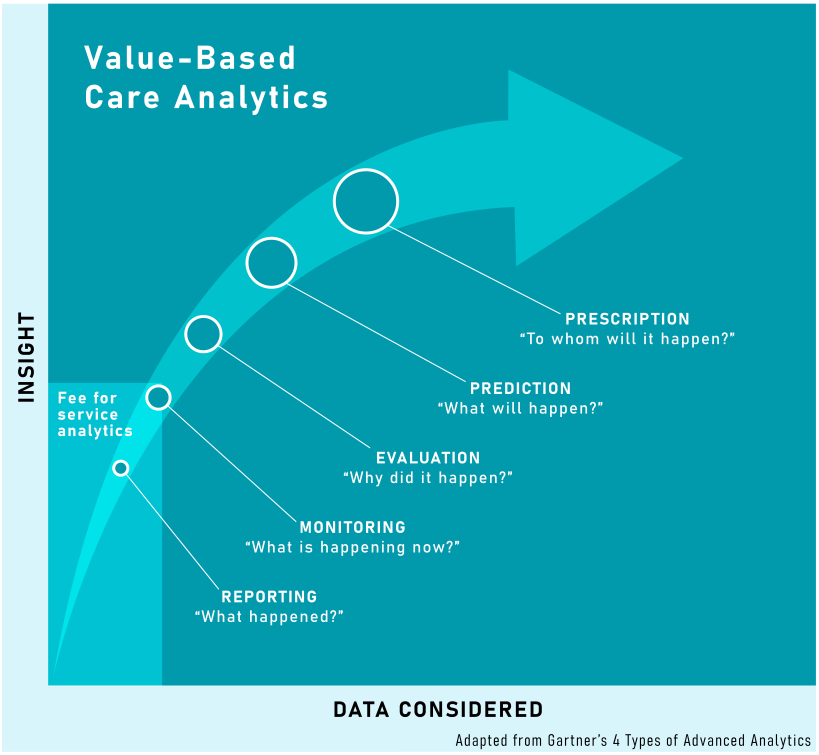


FIGURE 2.2: *Different approaches to data analysis in healthcare answer different kinds of questions on the way to value-based care.*

2.3 The benefits of Supervised learning

There are multiple factors that make supervised machine learning approaches more appropriate for the type of work that needs to be done in healthcare:

- First of all, it is more versatile than the traditional risk score approaches. By utilizing more data and more varied data, machine learning can be programmed to predict who is at high risk of needing urgent intervention regardless of their condition. It is especially relevant when different pieces of information are available across different populations. For example, a patient with a high-risk pregnancy who is not staying in the hospital may not meet some of the criteria, like length of stay or admission to the Emergency Department, that are used for the calculation of the risk scores. Machine learning is also more tolerant of missing or inaccurate data, the type of data that is present in healthcare.

- Since the model learns with new incoming data instead of making use of already acquired knowledge only, it can evolve to match new situations. This solves the issue of the patient population changing in response to the improvements in care. With medical staff trying to solve the problem of hospital readmissions, depending on the measures applied, the reasons for readmission of patients may change in response to these measures. Machine learning model can be retrained considering this new information and keep predicting the most actionable patients in real-time.

- By being able to analyse enormous amounts of complex data with a huge range of variables, known as "high dimensionality data" or "rich data", machine learning not only can find

hidden insights without being explicitly programmed where to look, but also spot important signals that humans would not and could not program a computer to spot [9]. This is arguably one of machine learning's biggest advantages: generating new knowledge from existing data.

2.4 Next generation: Deep learning

The rapid development in computer science and technology over the last decade resulted in boosted computing power (faster graphics processing and cloud architectures), increased availability of large datasets, and enriched theoretical understanding of AI. All of these enabled the development of new more complex AI algorithms, called neural networks [44]. These mathematical models have been inspired by the way that neurons process signals in the brain. They are trained to solve particular problems by extracting patterns and information from a set of data, without being specifically programmed how to achieve this. The most complex form of machine learning is called deep learning, which involves constructing a hierarchy of neural networks, which process input data as a huge series of interlinked, probabilistic calculations (see fig.2.3). When the algorithm is exposed to input data (medical image, scan, skin lesion picture, voice recording) to produce a specific kind of output (diagnosis, survival prediction, treatment recommendation), the model assigns weights to the features (variables) that associate inputs with the outputs. In the process of training the way the system interprets input data changes. There may be thousands of hidden features in such models with many levels of features that predict outcomes. This makes deep learning increasingly being applied for the detection of clinically relevant features in imaging data beyond what can be perceived by human experts [45, 46].

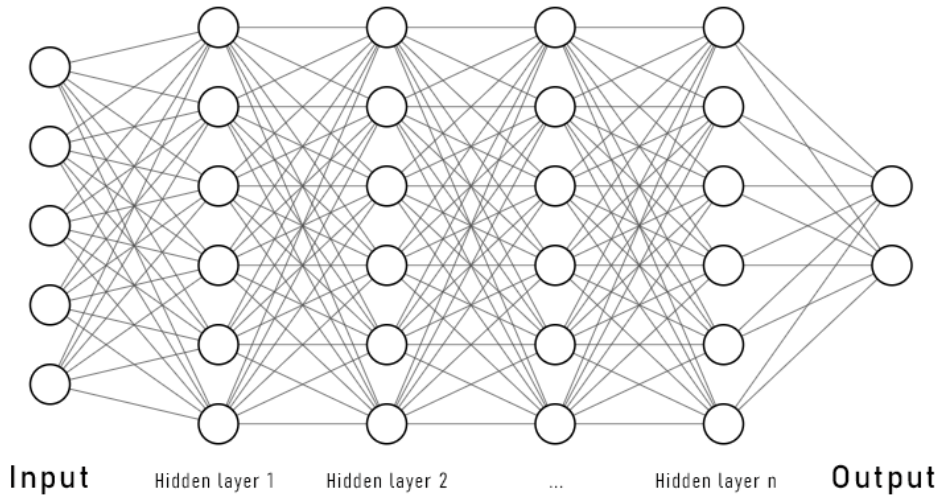


FIGURE 2.3: *The architecture of the neural networks. Deep learning constitutes many hidden layers that together perform complex calculations on the input data to produce the final decisions on the output.*

2.5 Machine learning applications in healthcare

2.5.1 Better than risk scores and humans

Over the last years, hundreds of studies across nearly all medical domains have shown that machine learning methods outperform traditional statistical approaches when it comes to predicting what is likely to happen, opening the path towards a value-based model of care. Furthermore, there are a number of studies proving that AI can perform as well as or better than humans at key healthcare tasks and reach 'expert level' or 'better-than-expert-level' performance in a number of practical applications, such as disease diagnosis [47–49]. According to statistics, there are about 12 million serious misdiagnoses given by the medical staff a year and this is where AI will have the biggest impact in transforming healthcare [50]. Today, machine learning algorithms are already outperforming radiologists by analysing CT, X-ray, and MRI scans faster and spotting malignant tumours more accurately than humans [51–53]. Similarly, in colonoscopy, small cancerous polyps can be missed by a human expert but are spotted by a machine [54]. Indeed, over 25% of medical scans return false negatives, which means some important signs of disease are missed [55]. This number could be brought down even to 1-2% by using machine learning [55, 56].

2.5.2 Less burden, more empathy

By improving the accuracy and speed of the diagnosis, AI can relieve some of the workload burden from the hands of medical professionals. For example, diagnosis of such conditions as glaucoma and diabetic retinopathy based on the analysis of the OCT scan of the eye structures can be done by AI in just under a few seconds at the local optician without the need for a doctor [57, 58]. Similarly, in the UK urinary tract infections (UTI) and skin rashes be diagnosed with deep learning more accurately, faster, and cheaper than at the doctor's after purchasing a test kit at the drug store [59, 60].

Additionally, beyond making a timely diagnosis, the ability of machine learning systems to analyse vast amounts of information far beyond the capacity of any one human, means that machine learning can save clinicians' time by liberating them from the time-consuming work of information gathering and medical analysis and allow them to focus on the personal elements of patient care instead. Indeed, the digitalisation of health records opened the opportunities for AI applications in healthcare, but also added a very time-consuming data-related workload for clinicians, who were not educated to do this kind of work. As a result, doctors and nurses became data clerks, leading to professional burnout, mental health issues and limited time to take care of their patients [61]. Meanwhile, the ritual of getting examined with empathy is important for patients to feel cared for and to build their trust in the doctor. A healthy relationship between patient and their doctor based on trust helps the patient's mental well-being and makes them more likely to adhere to the prescribed therapy [62]. If patients do not have trust in the healthcare system, they are unlikely to seek a consultation with a health professional until they need emergency assistance, which could have been avoided by prompt preventative measures. Therefore, it is critical for clinicians to be engaged with their patients and show empathy. These days doctors tend to be more absent, not having enough time to cultivate empathy, they are busy reviewing lab data and looking at the medical scans rather than giving the patient time to be listened to. AI could help empathy, which is a uniquely human quality, by giving the professionals more time and focus to interact with the patient, restoring the face-to-face contact, and as a consequence, rebuilding trust in a patient-doctor relationship. Studies show that clinicians who use digital documentation support software spend more time interacting with patients than those who do not [63–65]. For example,

in some centers in the UK and China, natural language processing software (a subtype of AI) liberates doctors from typing visit notes by translating their conversation with the patient into text, which also reduces the number of typing mistakes that could be otherwise propagated in the system [66–68].

2.5.3 Targeted medicine

Because AI systems are able to analyse a wider range of data and make connections that human clinicians might miss or not think to explore, they offer a way to handle the increasingly complex medical requirements of an ageing population by:

- identifying acutely ill patients at an earlier opportunity [69, 70] and ensuring that expensive medical interventions and treatments are used in a much more targeted fashion, before patients become seriously unwell,
- guiding researchers in how to construct cohorts for costly clinical trials
- making better predictions about future health that clinicians can act on to target prevention resources more effectively,
- making medical treatments more precise by reducing the number of unnecessary procedures and false diagnoses [71],
- avoiding invasive methods where other data can possibly predict the same outcome.

This way, AI could help healthcare systems become more sustainable, by improving patient outcomes while reducing costs. For example, a recent study at MIT suggests that the number of unnecessary surgeries could be reduced by 30% [72] by using machine learning to predict whether high-risk breast lesions on mammograms are in fact truly cancerous.

2.5.4 Reducing health disparities

There are currently substantial socio-economic differences in access to healthcare worldwide, with many rural populations experiencing substandard care [73]. AI could also help reduce these inequities by supporting the development of affordable preventive measures. In parts of Africa, where there is an absence of equipment and health professionals, people can take medical grade ultrasound scans of almost any part of the body (except the brain) using cheap smartphone software and have AI algorithm interpret them without the need for a health professional or technology they could not otherwise afford [74]. Furthermore, with the introduction of telemedicine, people from anywhere in the World can have more autonomy to generate their own data using different sensors (such as smartwatches) and lab test they can do at home ahead of algorithmic support to help free up healthcare professionals' time [75].

2.5.5 Application in mental health

Depression is now the number one cause of disability in developed countries [76]. There is no targeted therapy for patients to date, with treatment mostly relying on medications that often do not work. It takes a long time of trial and error before realising that the medication does not work resulting in many side effects for the patient and avoidable costs for healthcare. A more successful approach to treat depression is psychotherapy, but with a grossly insufficient number of professionals in the field, access to mental health care is very limited. Meanwhile, many people feel

more comfortable sharing their vulnerability with an avatar rather than with another human [55]. To address the issue of a lack of professionals and to accommodate the preference of people, smart machines that continuously track the person's state of mind can be developed, with first prototypes of human companions already underway [77]. These machines use AI to recognise cues about the state of mind from the person's speech (like tone and intonation), breathing patterns, vital signs, facial expressions, and behavioural patterns [78, 79]. Indeed, deep learning could find suicidal ideation cues from tone of voice, social media activity, and use of specific words in text (i.e. the use of the word "ibuprofen) and is much better at predicting suicidal attempts than a psychologist [80, 81]. AI could be employed to help find cues predictive of a suicidal attempt that the metal health professionals should pay attention to when interacting with the patient that they may not have thought about before.

2.5.6 The Future

Recent developments in medical screening technology and the emergence of new approaches in precision medicine, biopharmaceuticals, and medical genetics result in the production of highly complex big data that, when integrated with AI, will begin to deliver systematically personalised healthcare. Additionally, AI can further accelerate the progress of information-intensive tasks, such as the development of new drugs and genome sequence analysis. By integrating data from different systems, such as healthcare, social care, socio-economic information with data produced by these new technologies, AI will allow clinicians to get a much more precise grasp of patients' specific treatment needs and bring a better-suited personalised solution to the people with long-term care requirements. This means that the treatment of elderly people will go beyond acute care and focus on maintaining their quality of life and supporting independence instead. It is estimated that by 2040, AI will be able to integrate patient's test results and medical scans with data from wearables and connected devices at home, which will enable clinicians to make much better-informed diagnoses and even provide the patient with recommendations to take preventative measures, such as behavioural changes [9], [Own2]. Indeed, a lot of illnesses today are related to health behaviours (wrong diet, lack of exercise, smoking, etc.). A large study in Finland showed that people could be convinced to change their behaviour to practice healthier lifestyle once they had their genetic risk for heart failure calculated [82]. Machine learning could also produce customised diet recommendations by analysing personal gut microbiome, physical activity, dietary habits, amount of sleep and stress levels and combining these with the data from glucose sensors to help avoid spikes in glucose, insulin and triglyceride blood levels [83].

2.6 Challenges of AI application in Healthcare

There are multiple benefits to be realised from the use of AI in clinical practice. However, despite vast promising research, healthcare still lags behind other industries in machine learning utilisation with very few AI systems contributing to medical science or care to date [84]. There are just a few algorithms that were approved by the Food and Drug Administration (FDA) so far, (mostly in radiology to improve the accuracy and speed of image analysis) with no reimbursement provided for the investment into this technology. As mentioned before, the incentive to use data technology to provide better care faster and cheaper is already there. So are the data, tools, and equipment required for AI implementation. But, to make machine learning models applicable in clinics there is a whole set of issues that have yet to be addressed.

2.6.1 Healthcare Data

As previously mentioned, healthcare data comes with a set of challenges. In research, deep learning is developed and tested on big clean highly detailed data sets with labels (see fig.2.4). A good algorithm is accurate in its predictions, but it is not enough to make it work in the real world. Before the model can be widely deployed in healthcare systems, it's important to study its implementation on actual clinical data and make sure it can function safely and effectively. The real-world medical data usually comprises small datasets due to limited data sharing between institutions, restrictions in data access, under-representation of minorities in the patient population, differences in medical equipment used across sites, differences in data definitions, and rare use of more complex, expensive screening procedures. If machine learning is trained on datasets that do not fully represent the patient populations whose treatment they intend to support, they are at risk of introducing bias with the potential to distort healthcare outcomes rather than improve them. The risk of AI implementation is even higher since it has the potential to quickly hurt a lot more people than a doctor if they are wrong.

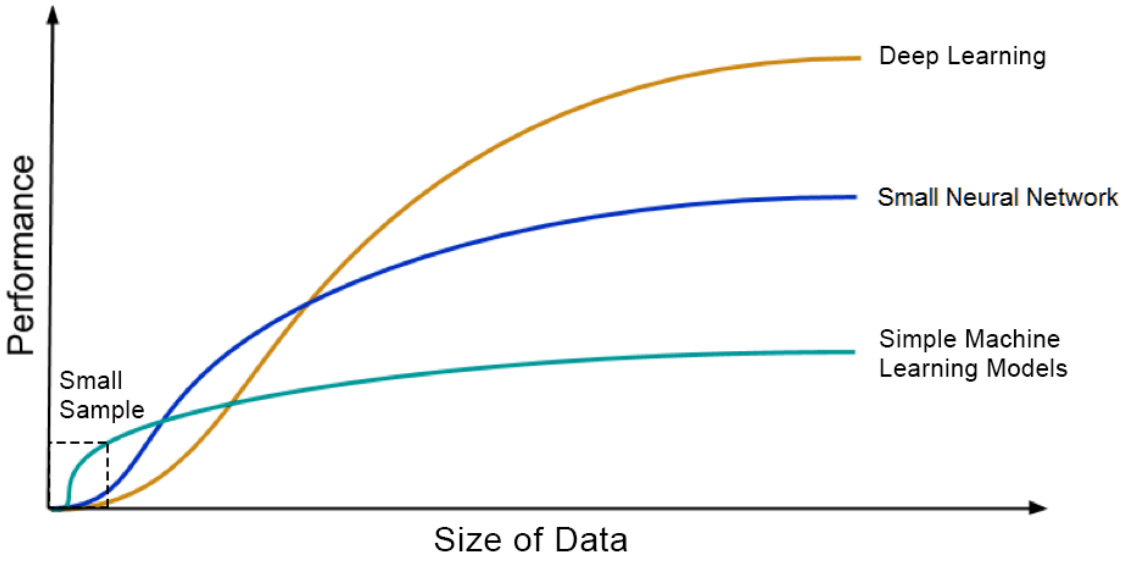


FIGURE 2.4: *Size of data and algorithm performance - problem with neural networks and small sample size.*

2.6.2 Digital readiness

Since AI relies on access to "rich" patient data, healthcare systems must be digitally ready to realise the full potential of AI-enabled healthcare. Digitalisation of healthcare data is well underway, but many institutions still heavily rely on paper records and pagers to manage patient care, which cannot be integrated into machine learning models. Furthermore, future applications of AI such as app-based voice-to-text transcription or treatment plan recommendations based on predictive analysis of medical records, test results, and genomics will require the integration of data from smartphones, wearables, and other digital devices with digital medical records. So, the AI model needs to be able to bring many different kinds of data together to produce one comprehensive outcome. It will also need to integrate seamlessly into existing clinical systems within hospitals and between primary and secondary care, which means that it needs to work on their specific data, be cost-effective, and be capable of working on machines with limited computational power.

2.6.3 Transparency

In comparison to earlier forms of statistical analysis, deep learning is much more computationally intensive and involves many stages of complex calculation with an additional downside of complex features in a deep learning model typically having little meaning to a human observer. As a result, the explanation of the model's outcomes may be very difficult or impossible to interpret. Meanwhile, for a clinician who will devise a patient's treatment plan, to be confident in the AI-driven decision, they need to understand how the algorithm reached their recommendations. Even though the mechanisms of clinicians' own decision-making processes are a "black box" with many biases, it is unlikely that a "black box" AI technology will be legally approved for use in medical care. It is possible that in the future, highly sophisticated AI systems may start making decisions of legal and moral consequence, such as delivering a medical diagnosis, which would raise new issues regarding liability, ethics, and compensation that the regulatory framework needs to be ready for.

2.6.4 Public confidence

The need for algorithms to be explainable extends beyond legal requirements. Public understanding of the new technology and how it uses their private data to improve their care is vital to ensure patients' confidence. AI-assisted healthcare cannot undermine the confidentiality of patient information or infringe on their rights to know how and why their data is being processed and must respect their right to opt out of sharing their data. At the same time, data analysts must ensure that the patients who opted out do not make the datasets unrepresentative for the algorithm training to avoid further exacerbation of inequalities in health outcomes. Although, the crowdsourcing of data through patient-facing apps shows that most patients are eager to record and share their data to make it work for them, the public needs to be informed about the benefits of AI-driven care to enable the less digitally aware groups to be in better control of their own healthcare [55]. Medical staff would also need education and training to be able to work with the new technology. Currently, there is still fear among medical professionals that AI systems could take over their jobs [85]. Instead, AI is aimed at supporting clinicians in making their work more efficient and delivering better-informed decisions. Cultural changes in healthcare will be required to enable AI implementation in clinical practice.

2.7 Realising the benefits of ML in healthcare

In summary, AI could greatly benefit healthcare by improving patient diagnosis and optimising clinical workflow and, consequently, help make the healthcare systems more sustainable and deliver better health outcomes for people. At the same time, the application of AI solutions in clinical practice poses a set of unique challenges that need to be addressed before AI-assisted healthcare can be successfully implemented in the real world. Ideally, to bring the maximum benefit to the medical practice, the AI-driven solution should meet the following criteria:

- Achieve diagnostic performance that is better than current state-of-the-art solutions and at least as good as a medical professional.
- Work on small highly complex data that can be realistically obtained in clinics (using low-cost non-invasive procedures that yield good quality data and can be performed on a wide population of patients).

- Go beyond simply diagnosing sick patients but identify who is actionable for preventative actions. To do this, the algorithm needs to be sensitive to very slight deviations from the norm that are present far before the appearance of any symptoms. If this could be achieved together with the ability to work with cost-effective procedures, AI could enable the delivery of a variety of screening procedures that would become a standard of care for people to monitor their health in advance of getting unwell.
- Bring complementary information together from a variety of sources (making best use of a variety of data available within and outwith healthcare systems) to obtain a more complete picture of the individual's health and enable a more personalised approach to delivery of treatment recommendations.
- Be transparent in how it reached the diagnostic decision by preserving the interpretability of features that were deemed important by the algorithm in producing the outcome. This is particularly important to ensure both, the patient's and the clinician's confidence in the recommendations provided and for the algorithm to be legally approved to support medical practice.
- Derive new insight into the mechanism of the disease by identifying important biological biomarkers that could not be spotted by the human observer. This way, AI would benefit scientific research by expanding our current understanding of health and disease.

2.8 Purpose and contribution of the project

The purpose of this project was to develop a machine learning solution that would deliver an automated diagnosis, focusing on Alzheimer's disease, and could in the future be realistically applied in clinical practice by aspiring to satisfy the conditions mentioned above. The model was applied to brain data which comes with further challenges (described in Chapter 3). This thesis goes through all the steps constituting the automated diagnostic system from patient scanning to diagnosis. The approach at every step is justified in light of building a feasible system that may in future be applicable in medical practice. Starting with the input data, data preparation for the model (making the best use of the data available), building the model, making a diagnostic decision, deriving new insight into the mechanism of the disease, and validating the model's performance. The process is divided into the following steps:

- In the section **3.4.1 Morphological network construction** on page 26 we introduce a new form of brain data that can be used as an input to a diagnostic pipeline while avoiding costly screening of patients, which makes it more applicable in clinical routine.
- Furthermore, in the section **3.4.3 Multi-layer Networks – Introducing Multiplex Structure** on page 27 we introduce a new data structure that brings further important information into the system, which could be valuable in making a correct diagnosis and contribute to the understanding of the disease progression. Our diagnostic system is capable of making the diagnosis using our proposed data structure.
- In the section **4.3.3 Previous works** on page 35 we describe our solution to combining data from multiple sources in a way that maximises the relevant information and minimises the noise when used as an input to the machine learning model for diagnostic purposes. Further, in the section **4.3.4 Newest Contribution** on page 35 we introduce our proposed machine learning pipeline that makes the best use of available data by combining feature fusion

methods from two different families: correlational methods and discriminative methods into one ensemble model.

- In the section **5.3.3 Analysis of early dementia biomarkers** on page 49 we derive new insight into the mechanism of Alzheimer's Disease progression across the brain at its early stages by identifying the most informative features for a successful patient diagnosis. This is possible due to the preserved interpretability of features in the framework.
- In the section **5.2 Results** on page 44 we test our framework on data from patients with early mild cognitive impairment and healthy controls to evaluate our framework's capacity to diagnose Alzheimer's Disease at the very early stages. We demonstrate that our system is sensitive to small changes in patients' brain morphology and outperforms the state-of-the-art solutions on the ADNI GO dataset.

Chapter 3

The problem of brain disease diagnosis

3.1 Challenges of brain data

In this project, we decided to focus on the difficult task of developing a machine learning algorithm capable of diagnosing the early stage of dementia, which is particularly challenging to diagnose by both, human clinicians and AI-assisted technology. Despite much success in AI-driven diagnosis of various conditions, AI application in psychiatric disorders diagnosis remains limited. This is due to the following considerations:

- We currently have many screening procedures available for various health conditions, the results of which can be analysed automatically. However, there is no routine screening available that would look at the health of the brain. Today, MRI scans of the brain are still rarely performed due to high scanning cost and noisy results that are hard to interpret. Also, image processing from raw image data is a multi-stage process, which can introduce errors and noise at each step [86]. This means that we have limited data for psychiatric disorders of the brain that would be available for the training of a potential machine-learning diagnostic algorithm.

- The lack of screening diagnostic procedures on the brain in turn leads to limited understanding of the brain function and the mechanism of psychiatric disease progression. The lack of knowledge about the brain compared to other parts of the body, is further exacerbated by the unique biology of the brain itself, which is a highly complex organ comprising billions of neurons [87].

- Furthermore, the structural arrangement of the neurons changes greatly over a person's lifetime, as it gets altered by learning and experiences, as well as injury and pathology [88,89]. So, at any point in time, the exact structure of each person's brain is inherently unique. This makes it very difficult to discern small changes in the neural connections that may lead to disease from harmless natural alterations.

- With high variability of neuronal arrangements in the brain within one patient and between different patients, it is especially challenging to model a healthy and disordered structure of the brain over a population of people. A successful diagnostic algorithm would therefore need to be highly flexible and applicable to data from a limited number of patients.

- The diagnosis is further complicated by the fact that many disorders of the brain do not fit within a binary classification of healthy vs diseased. More often the fluent nature of the changing brain results in a range of symptoms that would fit on a spectrum of disease severity

(i.e. autism spectrum disorder). This means that any potential classification of brain images relies on subjective measurements of symptoms or tests of ability that can introduce bias from the rater or the subject that would affect the performance of a potential diagnostic algorithm.

However, despite these challenges that are currently limiting the rollout of AI-assisted diagnosis in clinics, the advances in imaging technology, such as functional MRI and diffusion MRI, that allow for non-invasive in-vivo analysis of a patient's brain enable the researchers to analyse the structure and function of the brain in health and disease [90–92], [Own3]. The unique property of the brain, compared to other organs, is the complexity of the neuronal networks, which dictate how the brain functions. This means that it is important to understand the anatomical and functional changes beyond focusing on particular brain areas in isolation, but rather look at the connections between brain regions and how these are affected by the disease. Indeed, recently there has been a growing body of research in connectomics (a way of studying the connections between different parts of the brain), with more research papers being published every year (see fig.3.1) [2, 93].

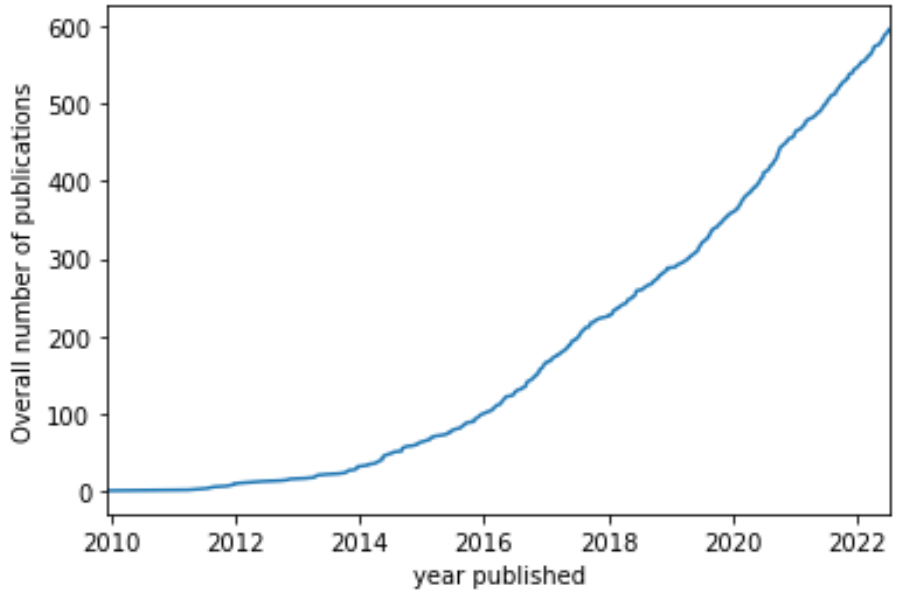


FIGURE 3.1: *The number of publications including the keyword "Connectomics" on Arxiv website increases every year.* [2]

3.2 Connectomics

3.2.1 Connectome extraction

A brain network, also known as a connectome, can be extracted from MRI scans of the brain. MRI is one of the most commonly used tests in neurology and neurosurgery as it provides a high level of detail of brain, spinal cord, and vascular anatomy. MRI makes use of the magnetization properties of atomic nuclei. The machine produces a strong magnetic field that makes the randomly oriented protons in the nuclei of water molecules inside the tissues align with the magnetic field. This alignment is then disrupted by the application of a Radio Frequency energy. In time, the protons go back into their alignment with the field, while emitting Radio Frequency energy. The frequency of this emitted energy is measured across different locations and converted into intensity levels, displayed as shades of grey in a matrix of pixels on the acquired image (see fig.3.2) [94].

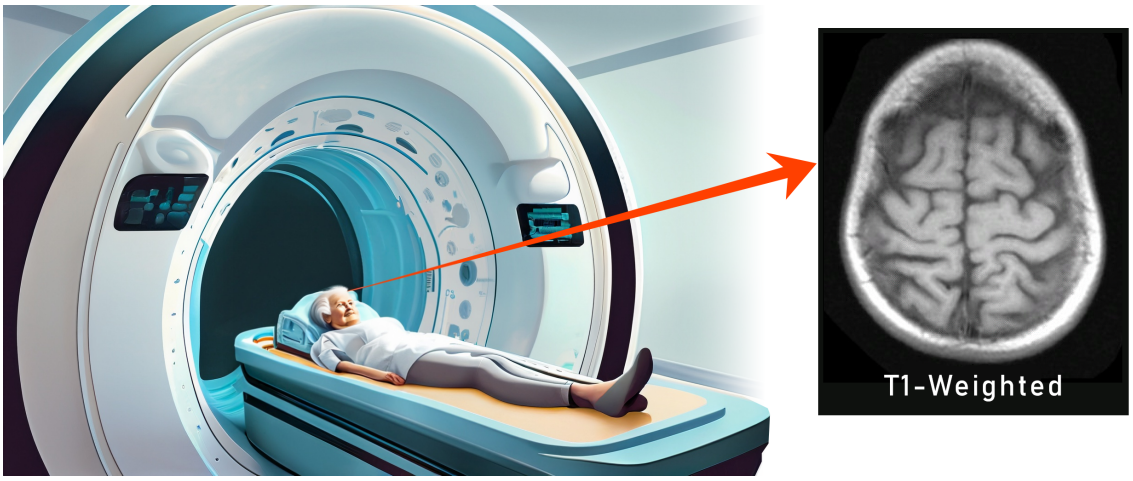


FIGURE 3.2: *MRI scanning procedure and image acquisition.*

By varying the sequence of Radio Frequency pulses applied and collected, different types of images are created. Repetition Time (TR) is the amount of time between the applications of consecutive Radio Frequency pulses. Time to Echo (TE) is the amount of time between the application of the Radio Frequency pulse and the acquisition of the echo signal. Tissues inside the body are characterised by two different relaxation times, a longitudinal relaxation time - T1 and a transverse relaxation time - T2. T1 measures the time taken by spinning protons to realign with the external magnetic field following the application of the Radio Frequency pulse. T2 measures the time taken by spinning protons to lose phase coherence among the nuclei spinning perpendicular to the main field [95].

The most common MRI sequences are T1-weighted and T2-weighted scans. T1-weighted images are produced by using short TR and TE times. Conversely, T2-weighted images are produced by using longer TR and TE times. A third commonly used sequence is the Fluid Attenuated Inversion Recovery (Flair). The Flair sequence is similar to a T2-weighted image except that the TR and TE times are very long. The brightness and contrast of the image are determined by the properties of the tissue imaged and the MRI sequence used (see fig.3.3) [94]. These MRI sequences are used to image brain morphology, for example, the thickness of the cortex or the volume of particular brain areas, which can be very useful for spotting structures such as tumours or serious anatomical changes due to tissue degeneration [96]. However, these images do not provide much information regarding changes in the underlying neuronal connections, which can be subtle and critical for early identification of a developing disease [97].

This can be achieved by Diffusion-weighted MRI (dMRI) and functional MRI (fMRI). In dMRI, the contrast of the image is generated by the diffusion (spontaneous movement) of water molecules in biological tissues [96, 98]. Molecular diffusion patterns reflect the interaction of moving water molecules with obstacles, such as macromolecules, fibers, and membranes, with water molecules diffusing more freely in the extracellular space compared to the intracellular space, where their movement is much more restricted. And so, these diffusion patterns can reveal the tissue architecture in microscopic detail. Because water diffusion becomes rapidly restricted in the ischemic brain tissue, dMRI is very useful in diagnosing acute vascular strokes in the brain [99]. More recently, diffusion spectrum imaging (a variant of dMRI) that can capture diffusion directions across fiber tracts and more accurate mapping of axonal trajectories has been used to derive structural connectomes (brain networks), in which each connection between two brain regions corresponds to the presence of fiber tracts linking them [100, 101].

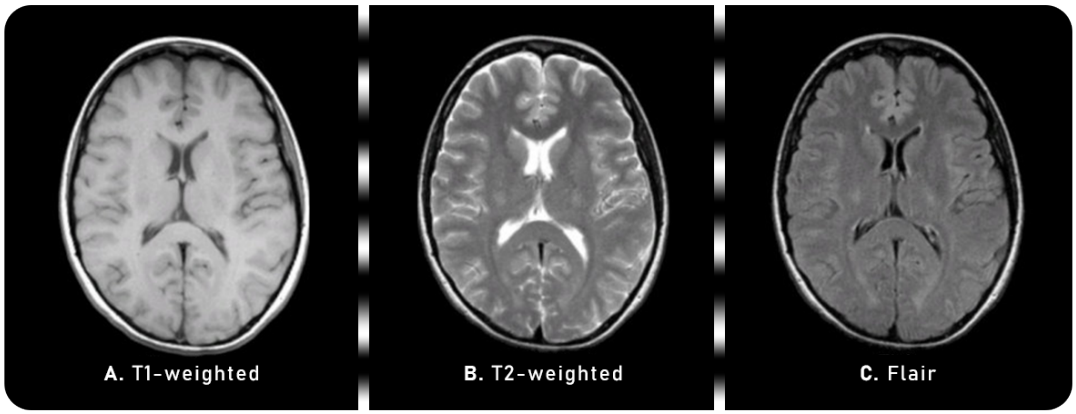


FIGURE 3.3: *Images of the brain produced by different MRI sequences.*

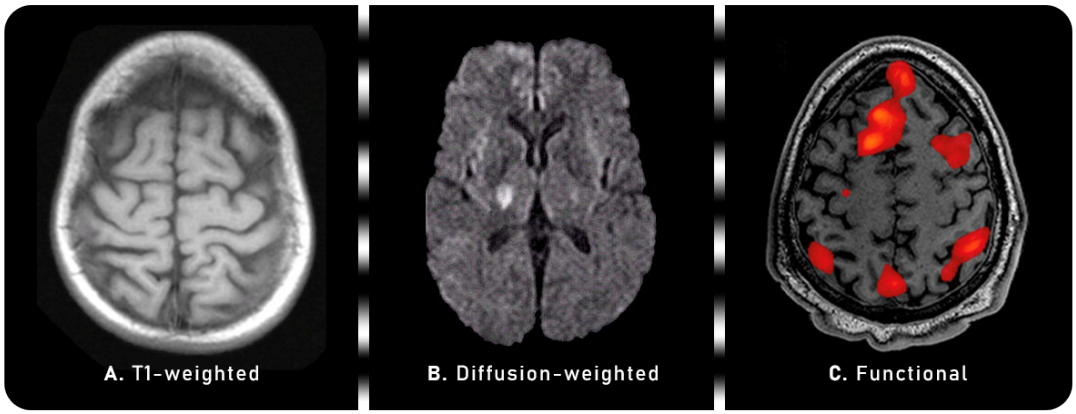


FIGURE 3.4: *Images of the brain produced by different types of MRI.*

fMRI, on the other hand, can measure brain activity by spotting changes in blood flow between brain regions [102]. When neurons are activated, the blood flow to those brain regions increases, bringing arterial oxygen-rich blood and displacing the venous oxygen-depleted blood [103]. Since, there is a pronounced difference in magnetic properties of oxygen-rich blood, which is more magnetic, and oxygen-depleted blood, which is resistant to magnetism, the blood-oxygen-level dependent (BOLD) contrast can be used to map neural activity in the brain. fMRI is mostly used by researchers to understand which parts of the brain are engaged in solving a task or activated in repose to external stimuli, but also to monitor brain activity in a resting state [104, 105]. The neuronal activity in resting brain states is attributed to the existence of a functionally connected default mode network. Resting-state fMRI can be used to model the functional connectome of the brain, in which each connection measures the strength of correlation in BOLD signal between two brain regions [97]. Any arising changes to the functional connectome that correspond to changes in brain function could signify the development of a disease.

3.2.2 Machine learning in connectomics

In recent years, researchers started exploring how machine learning can be used to analyse connectome data in order to predict clinical outcomes and analyse the function of subnetworks of the brain in health and disease [93]. Compared to other types of data that are more typically used for

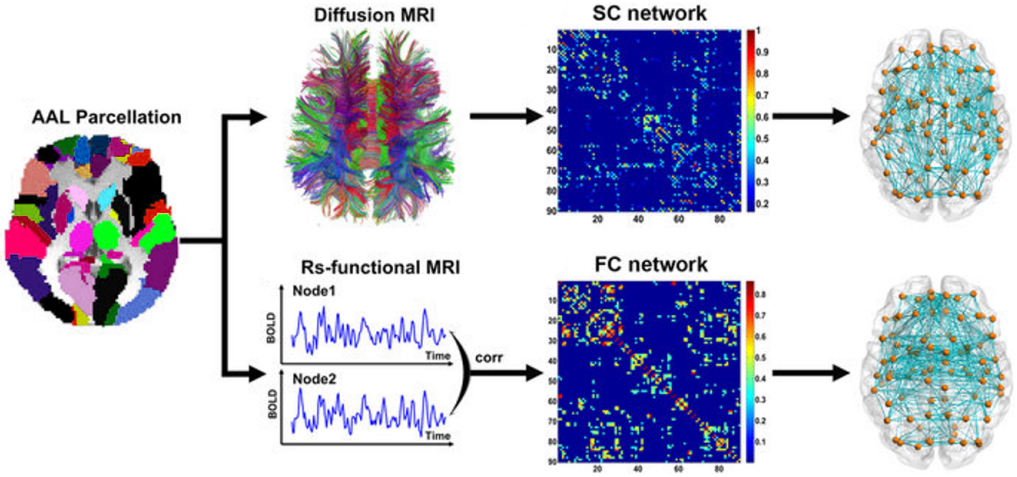


FIGURE 3.5: *Extracting structural and functional connectivity from dMRI and fMRI, respectively.* The process includes parcellation of the brain areas using an anatomical atlas, computing the signal between the brain regions, and constructing the connectivity matrices representing the connectome of the patient.

machine learning, connectome has unique properties, which present both special challenges and opportunities.

- Typically, medical images are grid-like with each pixel neighbouring only other pixels that are spatially nearby. Many kinds of features can be extracted from these images by machine learning models. Some of the examples include histogram of oriented gradient features, scale-invariant feature transform features, and learned convolutional neural network (CNN) features to name a few [106–108]. However, the features extracted from grid-like image data are inapplicable for use on network structured data of connectomes. Instead, in connectomes each brain region may be connected to any other brain region that is spatially close or far from it, with the features being defined based on the strength (and directionality) of the connection between these two brain regions.

- Connectomes have intrinsic correspondence both, between subjects and between multiple scans of the same subject. This provides a great advantage when interpreting diagnostic decisions made by the machine learning model as, once the connectomes are constructed, each brain region and each connection has a defined biological interpretation, providing an easy comparison between connectomes and their properties between different groups of patients (i.e. connectomes of healthy people versus connectomes of patients with disease) [93]. This is not the case for grid-like medical images, which need to undergo image registration to establish correspondence between individual voxels, which is entirely dependent on the frame of reference, making the biological interpretation of corresponding voxels difficult and unreliable.

- However, the construction of a connectome form raw MRI images is typically a multi-stage process, which can introduce noise at each step [109, 110]. Long acquisition time used for dMRI and fMRI scans leads to the introduction of noise already in the raw image before any further processing. This means that we need to include a step in the machine learning pipeline that will help extract meaningful features from connectomes while minimising the noise.

- Furthermore, high cost of dMRI and fMRI procedures means that many connectomics studies are performed and validated over relatively few scans compared to other types of medical data. Although connectomes typically have fewer features (also referred to as having fewer dimensions or being of lower dimensionality) than grid-like images (thousands of connections versus millions of voxels), this dimensionality is nearly always larger than the number of scans. This is the canonical problem in machine learning, knows as high dimensionality small sample size (HDSSS) problem, which can lead to poor performance of a machine learning model as it struggles to find the most informative features for the diagnostic task [111, 112]. This means that highly complex algorithms, such as manifold learning or neural networks, which deal well with high dimensional data, cannot be applied due to low sample size and simpler algorithms, such as K-Nearest Neighbour or Support Vector Machines (SVM) cannot be used without additional steps of feature selection, data augmentation, dimensionality reduction and model regularization [113].

There is, therefore, a need for a diagnostic system that would work on a small set of highly complex data specific to the brain that would be realistically applicable in clinical practice to automate patient diagnosis and further enrich our understanding of brain function and the development of the psychiatric diseases that could not have been otherwise realised by clinicians or researchers.

3.2.3 Focusing on dementia

Despite the undeniable benefits that connectome can bring to widen our understanding of brain wiring in health and disease, many challenges need to be addressed when building a diagnostic machine learning model on this data that could be applicable in clinics. In this project, we aimed to build a machine learning pipeline that tackles these issues and is capable of recognising brain disorders in the very early stages when the preventative measures can still be incorporated before the onset of the disease. The brain disease this study focused on is dementia. Dementia is a brain disorder that affects the way a person thinks, behaves, and interacts with others [114]. It is often a gradual process, and the symptoms can be difficult to notice at first. There is no one test to diagnose dementia, so doctors often use a variety of tests and assessments to make a diagnosis. Since dementia tends to affect elderly people most, it becomes an increasingly prevalent problem of the aging population Worldwide, reducing the quality of life and independence of the people it affects and putting a strain on the relatives who care for them and the resources of the social care services, which are already experiencing demand exceeding their capacity [115]. It is therefore critical to have screening procedures in place that would allow for early identification of pre-dementia states, such as early mild cognitive impairment (eMCI) and implementation of preventative measures to help keep a good level of independence and quality of life of patients for longer. eMCI, which may develop into Alzheimer's Disease (most common type of dementia) if left untreated, causes cognitive decline greater than that expected of the person's age and educational level [116]. There is evidence that eMCI alters brain structure and function that can be tracked in the connectomes extracted from the affected patients [117]. This makes the eMCI a perfect state to study using connectomics to enable early diagnosis and intervention.

3.3 Previous research

3.3.1 Brain connectivity in eMCI

Network analysis of functional and structural brain connectivity helped identify dementia biomarkers and brain connections affected by the neurodegenerative disorder [117]. [118] investigated the predictive power of various combinations of connectomic features, such as pairwise connectivity and maximum flow between two brain regions, extracted from dMRI images for eMCI and normal control (NC) classification problem. More recently, [119] computed sparse temporal networks using sliding-window approach over a time series of resting-state functional MRI. [120] extended this work by additionally considering the high-order correlation between different pairs of brain regions. By combining low-order and high-order brain networks, they further improved the classification accuracy of eMCI/NC patients. However, the main limitation of all these connectomic studies is that they relied on using functional or diffusion-based MRI, which are difficult to acquire as they are costly, time-consuming and prone to noise, which means they cannot be conventionally used in the diagnostic routine. Meanwhile, according to the tension theory of cerebral cortex morphogenesis, changes in the morphological attributes on the surface of the brain reflect the underlying changes in the structural and functional connectivity [121]. The morphology of the brain surface can be studied based on T1-weighted MRI images, which are much less costly and time-consuming to acquire than the other forms of brain imaging.

3.3.2 Brain morphology in Alzheimer's Disease

There is evidence that brain morphology is altered in Alzheimer's Disease. The progressing disease leads to the loss of grey matter in the brain, which is reflected on the brain surface in the form of a reduction of cortical thickness and widening of cerebral cortex sulci (groves in the outermost layer of the brain) [122]. For this reason and due to the easy acquisition of T1-weighted MRI images of the brain, many machine learning approaches for Alzheimer's Disease diagnosis used morphological features of the brain as biomarkers for identification of cortical neuroanatomical abnormalities in patients with Alzheimer's Disease. For instance, mean sulcal depth and width [122–124] had previously been identified as indicators for brain atrophy induced by Alzheimer's Disease. Moreover, [123] showed that sulcal depth and curvature are the most discriminative features between healthy subjects and patients with Alzheimer's Disease. On the other hand, [124] showed that the most distinguishing markers between these groups of people were the cortical thickness and hippocampal volume.

The changes in morphological brain properties associated with Alzheimer's Disease pathology were further observed in the early stages of dementia and could be used as biomarkers for early diagnosis of Alzheimer's Disease before the appearance of cognitive symptoms [125]. Previous research found that sulci in brains of MCI patients were characterized by reduced curvature, with sulcal widening observed and sulcal depth reduced compared to healthy subjects [122]. [126] demonstrated decreased global sulcal index and increased widths of nearly all individual sulci in MCI, while [124] found cortical thickness, the hippocampal volume and the sulcal width to be the best markers for distinguishing between MCI patients and healthy individuals.

However, none of these works investigated how different cortical features change in relation to one another in response to MCI to show how the connections between brain regions might be affected by early dementia.

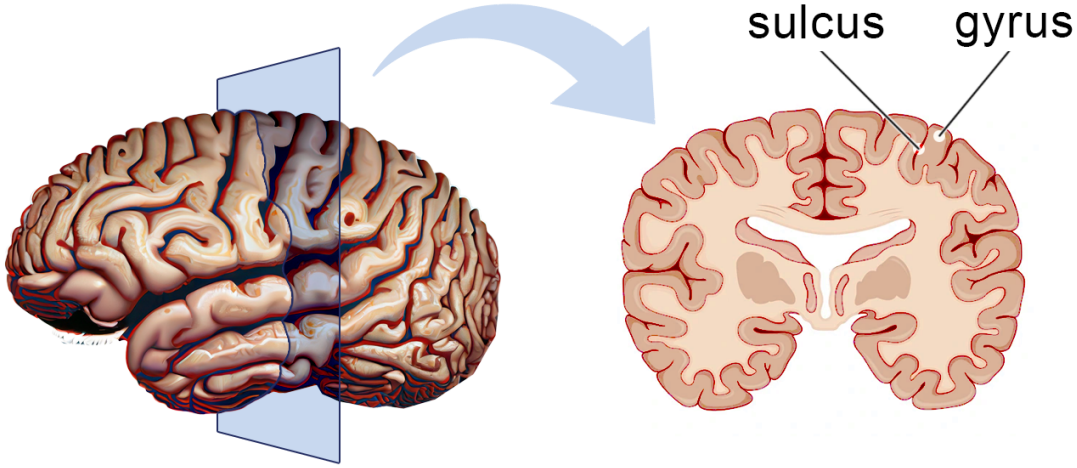


FIGURE 3.6: *The anatomy of the brain surface: Gyri (singular: gyrus) are the folds or bumps in the brain and sulci (singular: sulcus) are the indentations or grooves. Folding of the cerebral cortex creates gyri and sulci which separate brain regions and increase the brain's surface area and, as a result, improve cognitive ability.*

3.4 The proposed morphological data structure

3.4.1 Morphological network construction

Considering the fact that communication between different brain regions is key for proper brain function and to make use of relatively easy acquisition of information about brain morphology, we decided to study how morphological connections between brain regions differ between healthy people and patients with eMCI. To do so, We proposed to use various shape measurements of the brain surface and construct a network that compares the shape of the cortex between different brain regions.

We specifically focused on the following measures, as explained in [127] extracted using the Free Surfer tool [128]:

- Maximum principal curvature - The principal curvature measures the extent to which cortical surface bends in different directions at a specific point on that surface. If there are many curves passing through a point on the surface, then the curve with the highest curvature value defines the maximum principal curvature.

- Cortical thickness - Cortical thickness measures the thickness of the brain grey matter and was computed by calculating the average shortest distance between the GM/WM and GM/CSF surfaces.

- Sulcal depth (sulcation) - Sulcal depth holds information on how far a point on the surface is from a hypothetical surface existing midway between the sulci (folds) and the gyri (crevices) in the brain. Sulcation is defined by calculating the dot product between the displacement vector from this 'mid surface' and the surface normal.

- Average curvature - The average curvature of a surface at a specific point is defined by averaging the principal curvatures at that point, i.e. the average between the maximum principal curvature and the minimum principal curvature.

3.4.2 Definition of the morphological brain network

In line with the works of [129] and [130], we define morphological brain networks as follows. For each cortical attribute (e.g., cortical thickness), we build a single-view network for each subject. Such network comprises a set of nodes (anatomical brain regions) and a collection of edges interconnecting the nodes (representing the dissimilarity between the two brain regions in morphology). The average value of a cortical attribute was calculated for each anatomical region of interest (ROI). For each cortical attribute, the strength of each network edge connecting two ROIs is then computed as the absolute difference between their average values, thereby quantifying their dissimilarity (see fig.3.7). The same procedure was followed to obtain the connectivity matrices from different cortical attributes (e.g., sulcal depth, curvature). We note that morphological brain connectivity models dissimilarity in morphology between anatomical brain regions (similarly to functional connectivity, which models correlation between firing neurons), rather than being a real physical connection (like structural connectivity). We believe that both functional and morphological connections mediate 'real' connections, as there is a relationship between brain function, morphology, and structure [121].

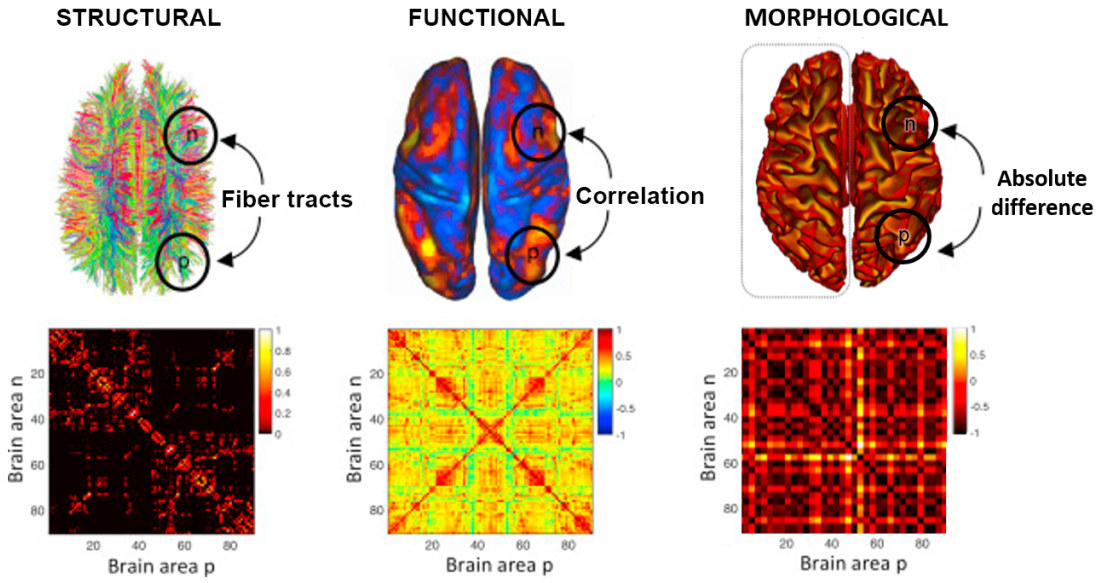


FIGURE 3.7: *Construction of structural, functional and morphological networks. Each cell in the connectivity matrix calculates the relationship between two brain regions.*

3.4.3 Multi-layer Networks – Introducing Multiplex Structure

For each subject, We therefore constructed four morphological networks, which we will refer to as single morphological views: maximum principal curvature network, cortical thickness network, sulcal depth network, and average curvature network. Next, we need to make sure that we make the best use of the information contained in this data for my eMCI diagnostic task. To do this, we construct a multi-layer network (a multiplex), consisting of multiple morphological views.

Previous research showed that using multi-layer networks (i.e., stacking different networks) improved the prediction accuracy for disease identification when compared to using single-view

networks. Some of these works included the classification of NC/MCI/AD using a combination of features from MRI, PET, and CSF [131], structural inter- and intra-subject brain similarities in MRI [132], both confirming that multiplex network features yield better classification results in comparison to using low-level features. Other works used multiplexes for simultaneous analysis of anatomical and functional brain networks [133] and varied frequency in fMRI to find important functional brain regions affected by schizophrenia [134]. However, none of these multi-layer network-based methods explored the relationship between two consecutive layers in the network of cortical morphology [93]. Specifically, to the best of my knowledge, no previous method explored the similarity between layers in a typical multi-layer network for modeling brain connectivity for early dementia diagnosis [93]. To fill this gap, we proposed a multi-layer network (multiplex), consisting of multiple morphological brain network views [Own4].

We noted that a simple concatenation of multiple networks hinders the investigation of potentially complex changes in cortical regions, which might vary jointly or independently across different brain views as they become affected by dementia onset. Hence, we introduced inter-layers into a multiplex structure to capture the relationship between different brain views. Since each multiplex is not invariant to the ordering of the intra-layers, in my previous research [Own4], we generated multiple multiplexes for each subject while considering all possible combinations of intra-layers, thereby capturing all relationships between different brain views. However, this resulted in highly correlated data and many redundant features. To address this limitation, in this work [Own5], we proposed a new shallow multiplex structure, each consisting of two morphological views with a single inter-layer between them (see fig.3.8).

3.4.4 Convolutional brain multiplex construction

In a generic way, we define a brain multiplex $\mathcal{M}$ using a set of M intra-layers $\{\mathbf{V}_1, \ldots, \mathbf{V}_M\}$, each representing a single view of the brain morphology, (i.e., cortical attribute), where between two consecutive intra-layers we slide an inter-layer $\mathbf{C}_{i,j}$, which is defined by convolving two consecutive intra-layers. The convolutional inter-layer models the relationship between two layers. More specifically, the convolution 'blends' two layers together and is the expression of the amount of overlap of one layer as it is shifted over another. Each element in row a and column b within the convolutional inter-layer matrix $\mathbf{C}_{i,j}$ between views $\mathbf{V}_i$ and $\mathbf{V}_j$ is defined as: $\mathbf{C}_{i,j}(a,b) = \sum_p \sum_q \mathbf{V}_i(p,q)\mathbf{V}_j(a-p+1, b-q+1)$.

The multiplex architecture allows us not only to explore how different brain views get altered by a specific disorder but also how their relationship might get affected. Since the morphological brain connectivity matrices are symmetric, we extract features from each multiplex by directly concatenating the off-diagonal weights of all connections in each triangular matrix. For each network of size $n \times n$, we extract a feature vector of size $(n \times (n-1)/2)$.

In [Own4], we introduced the generalised multiplex architecture:

$\mathcal{M} = \{\mathbf{V}_1, C_{1,2}, \mathbf{V}_2, \ldots, \mathbf{V}_j, \mathbf{C}_{i,j}, \mathbf{V}_j, \ldots, \mathbf{V}_M\}$. We note that, for a specific multiplex, we were only allowed to explore similarities between consecutive layers. To explore the inter-relationship between all possible combinations of intra-layers, we generated for each subject N multiplexes by simply reordering the intra-layer networks, thereby generating an *ensemble multiplexes* $\mathbb{M} = \{\mathcal{M}_1, \ldots, \mathcal{M}_N\}$. However, this approach resulted in many highly correlated features used for ensemble learning, which may adversely affect the model's performance. To minimize the correlation between different multiplexes, we proposed a shallow (i.e., 2-layer) convolutional multiplex structure [Own5].

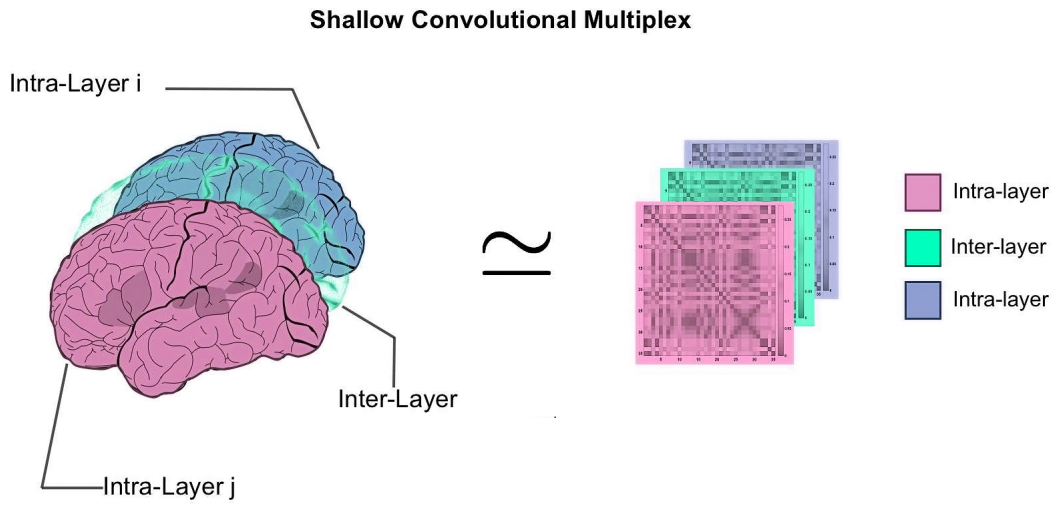


FIGURE 3.8: *The representation of the multiplex where the inter-layers are created between two intra-layers (two morphological brain networks derived from the cortical surface)* Figure adapted from [Own7]

We define a *shallow* multiplex $\mathcal{M} = \{\mathbf{V}_i, \mathbf{C}_{i,j}, \mathbf{V}_j\}$ using 2 intra-layers $\mathbf{V}_i$ and $\mathbf{V}_j$ and an inter-layer $\mathbf{C}_{i,j}$ encoding the relationship between $\mathbf{V}_i$ and $\mathbf{V}_j$, slid in between them (see fig.3.8). We note that each subject-specific brain multiplex in $\mathbb{M}$ captures unique similarities between 2 different morphological brain network views (e.g., sulcal depth network and cortical thickness network) that are not present in a different shallow multiplex.

Fusing information from different brain multiplexes is crucial for more accurate identification of the demented brain state since, each brain multiplex captures a unique relationship between brain views, which can help unravel the complex nature of brain disorders for more accurate diagnosis. In the next chapter, we discuss the proposed ways of fusing the data for use in the machine learning model for dementia diagnosis.

Chapter 4

Machine Learning Pipeline

This chapter describes my proposed machine learning pipeline. Machine learning, much like a human student, needs to learn a set of rules that define the way of solving the diagnostic task (by finding common characteristics of the disease) rather than memorising the information that is specific to the dataset. This means that new data will not change the method and the rules learnt by the algorithm can be applied to another cohort of patients. To learn this skill correctly, the algorithm must have access to holistic data. To prepare the patient information for a diagnostic task, we need to combine the data from different multiplexes and identify a subset of features that represent the dataset well and are most useful in helping the machine learning algorithm distinguish between patients with early dementia against the healthy subjects. Then we need to choose the right algorithm to work with our data. As previously mentioned, there are several different approaches that can be used to extract useful features from the data that will serve as an input into the machine learning algorithm and the choice of approach depends on the data available and the task at hand.

4.1 Introduction to feature extraction

In my case, we want to distinguish between healthy adults and patients with eMCI. It is a 2-class classification task. In classification, we try to find a boundary that separates patients from different groups. Each patient is a data point in a group. We want to separate the patients into 2 classes based on some characteristics of their brains (Healthy vs. Dementia). These characteristics, in the context of machine learning, are called "features". As described in the previous chapter, our features comprise morphological connections between different brain regions and the relationship between brain networks that are based on various cortical attributes.

In clinics, it is important to understand how the model came up with a diagnostic decision. Usually, when biological interpretation of the outcome is important, the features would be extracted from the data by a human professional and used to train the machine learning model. For example, based on their medical knowledge, a clinician knows that the measure of the thickness of the cortex in a specific area of the brain is an important factor in assessing whether a patient has dementia. The machine learning algorithm is trained to decide the importance of these features and make a diagnostic decision by weighing the relevance of each feature in solving a given problem. The main advantage of this approach is that simple machine learning models can be used, reducing the requirement for the amount of data needed for training. Also, the transparency of decision-making is preserved, making it possible to validate the results and identify biomarkers of the disease (a measurable indicator of a biological condition, whether it is a normal or pathogenic state).

The problem with this approach is that it can only be applied to areas where there is already substantial scientific knowledge required to extract these features and the contribution to this knowledge by the machine learning algorithm is limited as it is only exposed to the features that were previously found important in solving the problem. This approach may omit other features, that were not previously identified as biomarkers, but may also be important for the diagnosis. Since our knowledge of the importance of morphological connections in dementia is very limited and we want to contribute to the body of scientific knowledge in the area, this approach is not optimal, and a better solution would be to find a machine learning algorithm that is capable of finding the biomarkers of early dementia without the need of human intervention.

On the other hand, more complex ML algorithms, such as neural networks, can extract their own features from the data and assign weights to these features to make a diagnostic decision. The main benefit of these algorithms is that they can be applied to complex problems that cannot be solved by simple algorithms applied on a limited set of predefined features, which makes it a better fit for our difficult problem of distinguishing between healthy subjects and patients with very early signs of cognitive impairment. However, the downside of neural networks is that the process of feature extraction and decision-making involves many calculations, which makes the features extracted from the data by the neural network hard to interpret and the decision made harder to validate. As a consequence, even though the algorithm may work well in making a correct diagnosis, the insights about the biological factors that contributed to the decision are not understood. Furthermore, complex machine learning models need big data sets for training due to the complexity of the calculations involved. Both of these issues limit the applicability of these types of models in clinics, where the reason for a specific diagnosis needs to be understood. Therefore, we need another approach to extract meaningful features from our data to make the diagnosis.

4.2 Combining data from modalities

In our proposed solution we seek a middle ground between simple and complex algorithms by incorporating feature extraction from our multiplexes as part of the machine learning pipeline. Since we have data from multiple modalities, we need a method to combine the data in such a way that we get the most informative features from each modality. There are three different ways of combining the data from different modalities: raw data level, feature level or decision level [135]. Raw data fusion works for bringing together information from homogenous data sources, which makes it inapplicable in our situation.

4.2.1 Feature Level Fusion

In feature level fusion, raw data is converted into quantitative feature representations, which are combined using concatenation, kernel-based methods or dimensionality reduction, to bring these feature representations into a joint subspace where the classification task can be performed [136]. Most existing network fusion methods use concatenation of features extracted from different brain networks [93]. In feature concatenation, the feature vectors from different modalities are stacked together to form one long feature vector. This is the simplest way of fusing multimodal data, but it may result in data with higher dimensionality from one modality (data with a longer feature vector) to dominate over data with lower dimensionality from another modality (data with a shorter feature vector) [137]. Kernel-based methods address this issue by transforming the data from different modalities into a joint higher dimensional space, where the data is then fused [138, 139].

However, both approaches are not suitable for a dataset with a low sample size, as they result in data with very many features, contributing to the curse of dimensionality, where a low sample size of highly dimensional data results in an unreliable classifier's performance. Given modality-specific noise, we risk unstable feature selection by the model and overfitting to the dataset, which would make the diagnostic model unreproducible on new data [140]. To overcome these limitations, we need a feature fusion method that extracts the most relevant features for the classification task, minimises the modality-specific noise and reduces data dimensionality.

4.2.2 Decision Level Fusion – Ensemble of Classifiers

In decision level fusion one can overcome the problem of combining data from heterogenous data sources by making the classification decision based on each data channel separately and then combining the outcomes into the final diagnostic decision [141]. Specifically, in ensemble learning multiple sets of features can be used to train many different classifiers independently and further fuse the data on a decision level. An ensemble of classifiers is a set of classifiers whose individual predictions are combined to classify new examples. Different classifiers of the ensemble can be generated by manipulating the training set, manipulating the input features, manipulating the output targets or injecting randomness into the algorithm [135]. Previous research showed that ensembles tend to be more accurate than the individual classifiers that make them up [142, 143], as they can overcome the limitations of the simple individual algorithms used, for example:

- Ensemble can provide a good approximation of the target function when the true target function cannot be represented by any of the hypotheses (i.e. by taking a weighted sum of these hypotheses) [135, 143].
- Ensemble of classifiers can also help alleviate problems connected to the imperfectness of the learning algorithm used by allowing for the combination of multiple linear classifiers for the classification of linearly inseparable data, while keeping the simplicity of the model, instead of using a highly nonlinear classifier [143].

On the other hand, ensembles can address the problems connected to using more complex learning algorithms, such as neural networks:

- When only a small data set is available for training, many different hypotheses can give the same accuracy on training data. Ensemble might alleviate this problem by taking an average of these hypotheses [135].
- By combining multiple classifiers, ensemble learning reduces the sensitivity to the shape of the training data due to its limited size, avoiding overfitting and leading to a better generalisation of the trained model [143].

This gives the ensemble learning advantages over simple and complex algorithms when little data is available for a difficult classification task, where the boundary between classes (i.e. different diagnoses of healthy versus early dementia) is hard to reliably establish by making the best use of the data at hand. A good diagnostic performance could be achieved by feeding data from different modalities into separate classifiers and then combining them using the decision level fusion method to obtain a diagnostic decision. However, if we wanted to apply this method on its own to the raw data, we would lose important information about the relationship between features from different modalities, which may be important for making the diagnosis and could contribute to a better understanding of the disorder. Therefore, we seek a combination of feature fusion methods that

will lead to an accurate diagnosis on a small dataset, while contributing to the existing body of research on the mechanism of early dementia onset by making the best use of morphological brain data from different modalities.

4.3 Proposed solutions

Since each multiplex captures a unique and complex relationship between different brain network views, one needs to examine all morphological brain multiplexes for each patient. This should provide a more holistic understanding of how explicit morphological brain connections can be altered by dementia onset, as well as, how their implicit high-order (a connection of connections) relationship can be affected. To make use of all the information available from different multiplexes, we seek a feature fusion method that would extract the most relevant features for the classification task, minimise the modality-specific noise and reduce data dimensionality. Indeed, a prevalent practice for improving classification accuracy is to identify features which contain useful information for the classifier training by reducing redundant features and primarily focusing on features which have been scrutinised, especially with the growing dimensionality and complexity of data. The existing approaches can be categorised into two primary groups: methods that seek to identify the most discriminative features and methods that aim to identify highly correlated features in the data.

4.3.1 Discriminative methods

The first group, discriminative machine learning approaches, aim to maximise the distinction between sets of data allowing for a reduction in dimensionality. There are several discriminative approaches, such as Linear Discriminant Analysis (LDA) [144], where the input features are projected onto a space where their disparity and discriminability are maximised. These were previously used to predict Alzheimer's disease progression from structural imaging [145]. Other methods include discriminative feature selection methods such as Mutual Information (MutInf-FS) [146], which prioritises minimising the redundancy in data while maximising the dependency and relevance of features, or Multi-Cluster Feature Selection (MCFS) [147], which reduces the data dimensionality while maintaining its structure. Other approaches such as Infinite Feature Selection (Inf-FS) [129,148] model the relationship between sets of features using a graph to identify groups of highly connected discriminative nodes.

4.3.2 Correlational methods

The second group, correlational methods, aim to identify highly correlated features within the data, selecting a subset of features from the original data with the purpose of removing redundancy which might hinder prediction accuracy. A wide body of correlational methods can be covered with canonical correlation analysis (CCA) [Own4,Own5], [149,150] and its variants. CCA, broadly speaking, maps input features into a shared space where features are more comparable and hence, their correlation can be maximised. The projected correlational features in the shared space are then fused together, which reduces the dimensionality of the original data. CCA was shown to be especially efficient in analysing and fusing associations between two sets of variables [149,151] by identifying the structure common to the two data sources and creating a subspace that is robust to noise from different modalities. Since CCA aims to find such subspace that the correlations between projected features are maximised, the noise present in either modality that is uncorrelated with the other modality should be absent in the projected subspace [136]. CCA was shown to

yield more discriminative features than any of the input feature vectors alone or their simple concatenation [149]. Several CCA variants have been developed including sparse CCA (sCCA) [152] and non-linear kernel CCA (kCCA) [153]. Specifically, with the proliferation of multi-view data, multi-view CCA (MvCCA) [154, 155] and Tensor CCA (TCCA) [156] were designed with the aim of maximising the correlation between an arbitrary number of views. In addition to these, there are several innovations upon existing CCA variants such as two-stage kernel CCA (TSKCCA) [157] which by implementing L1-regularization allows for the identification of more complex non-linear correlations, improving upon kCCA and other existing CCA methods.

4.3.3 Previous works

In my previous work [Own4], we used CCA to map two sets of brain connectomic features into a shared space in preparation for eMCI/NC classification. However, since my data had many features causing the high-dimensional covariance matrix singularity problem [158], the CCA could not be used without previously applying a dimensionality reduction technique. Therefore, we first applied Principal Component Analysis (PCA) to my data, before fusing it using CCA. PCA is an unsupervised dimensionality reduction method, which projects the original data onto a lower dimensional space along the principal directions reflecting the highest variation in the data. First, the mean of the dataset is computed for each feature and subtracted from all the data points to identify the centre of mass. Then, a covariance matrix is computed for the centre of mass and the eigenvectors and their corresponding eigenvalues are found. Finally, the data is projected along the leading eigenvectors (directions of maximal data scatter). PCA was previously shown to positively affect the classification performance when using morphological features for MCI diagnosis [159].

The main limitation of this approach is that even though the classification accuracy of the machine learning algorithm is improved, the biological interpretability of the results is limited as we project data without performing feature selection or taking the relationship between the views into account [158]. Sparse CCA was shown to address this issue by computing the relationship between modalities using much fewer features [160]. Although sparse CCA does not take the structure of the data into consideration, previous research [158] on genomic data has shown that adding additional structure constraints to sparse CCA can result in improved selection of bacteria associated with environmental variables. Since connections in the brain tend to be affected jointly by a disease, including the initial structure of the data in the process of modalities mapping and feature selection should provide more information about the mechanism of disease progression and may improve eMCI/NC classification performance. Therefore, in my paper [Own5] we proposed to use the recently developed Structured Sparse CCA (SS-CCA) [161, 162] for feature level fusion for the task of eMCI/NC classification, which allowed me to identify the most important features for the diagnostic decision that may be biomarkers of early dementia.

4.3.4 Newest Contribution

Previous research on dementia classification either used methods that identify discriminative connectional features [129] or methods that identify highly correlated features [Own4] as described above. A fundamental limitation of such approaches is that they disentangle correlational from discriminative methods, which might limit our understanding of disordered connectional changes in the diseased brain by overlooking the complementary information that can be integrated from both approaches to further improve the eMCI/NC classification accuracy. To fill this gap, we propose an ensemble pipeline for parallel feature mapping and selection that incorporates both

the correlational and discriminative approach to extracting relevant information for the diagnostic task from the input data.

Correlational block

To make use of all the information available from different morphological brain multiplexes, we need to examine all multiplexes in the ensemble $\mathbb{M}$. Building on our previous work [Own4], in the correlational learning block of our framework (see fig.4.1), we first pair brain multiplexes, each generated using a different set of morphological brain views and apply CCA [149, 150] to map these pairs of multiplexes into a shared subspace that depicts highly-correlated relevant features. As described in [Own4]:

Suppose that $\mathbf{M}_k \in \mathbb{R}^{d \times N_s}$ and $\mathbf{M}_l \in \mathbb{R}^{d \times N_s}$ are two training multiplex feature matrices derived from two different multiplexes in $\mathbb{M}$, where N_s denotes the number of training samples. For each pair of multiplexes $\mathbf{M}_{k,l} = [\mathbf{M}_k, \mathbf{M}_l]$, we define their covariance matrix

$$\mathbf{\Sigma}_{k,l} = \begin{pmatrix} cov(\mathbf{M}_k) & cov(\mathbf{M}_k, \mathbf{M}_l) \\ cov(\mathbf{M}_l, \mathbf{M}_k) & cov(\mathbf{M}_l) \end{pmatrix}$$

where $cov(\mathbf{M}_k) = \mathbf{M}_k\mathbf{M}_k^T$ denotes the within-set covariance matrix of $\mathbf{M}_k$, and $cov(\mathbf{M}_k, \mathbf{M}_l) = \mathbf{M}_k\mathbf{M}_l^T$ denotes the between-set covariance matrix of $\mathbf{M}_k$ and $\mathbf{M}_l$. To map both training multiplex matrices onto a space where the respective distributions of their features are more 'aligned' and easily comparable, we aim to maximize the pair-wise correlation across the two matrices $\mathbf{M}_k$ and $\mathbf{M}_l$:

$$corr(\hat{\mathbf{M}}_k, \hat{\mathbf{M}}_l) = \frac{cov(\hat{\mathbf{M}}_k, \hat{\mathbf{M}}_l)}{var(\hat{\mathbf{M}}_k) \cdot var(\hat{\mathbf{M}}_l)}$$

where $\hat{\mathbf{M}}_k$ denotes the linear CCA mapping of the multiplex feature matrix $\mathbf{M}_k$ to the canonical shared space using the estimated transformation matrix $\mathbf{W}_k^T$ such that $\hat{\mathbf{M}}_k = \mathbf{W}_k^T\mathbf{M}_k$. Similarly, the second set of training multiplex features $\mathbf{M}_l$ is mapped using the estimated transformation matrix $\mathbf{W}_l^T$. More precisely, $cov(\hat{\mathbf{M}}_k, \hat{\mathbf{M}}_l)$ is defined as $\mathbf{W}_k^T cov(\mathbf{M}_k, \mathbf{M}_l)\mathbf{W}_l$, $var(\hat{\mathbf{M}}_k)$ as $\mathbf{W}_k^T cov(\mathbf{M}_k)\mathbf{W}_k$, and $var(\hat{\mathbf{M}}_l)$ as $\mathbf{W}_l^T cov(\mathbf{M}_l)\mathbf{W}_l$.

Both canonical transformation matrices are estimated through maximizing the covariance between the mapped multiplex feature matrices $\hat{\mathbf{M}}_k$ and $\hat{\mathbf{M}}_l$, constrained to $var(\hat{\mathbf{M}}_l) = var(\hat{\mathbf{M}}_k) = I$, using Lagrange multipliers. This is achieved through solving the following eigenvector equations:

$$\begin{cases} cov(\mathbf{M}_k)^{-1} cov(\mathbf{M}_k, \mathbf{M}_l) cov(\mathbf{M}_l)^{-1} cov(\mathbf{M}_l, \mathbf{M}_k)\hat{\mathbf{W}}_k = \mathbf{\Lambda}^2\hat{\mathbf{W}}_k \\ cov(\mathbf{M}_l)^{-1} cov(\mathbf{M}_l, \mathbf{M}_k) cov(\mathbf{M}_k)^{-1} cov(\mathbf{M}_k, \mathbf{M}_l)\hat{\mathbf{W}}_l = \mathbf{\Lambda}^2\hat{\mathbf{W}}_l \end{cases}$$

where $\hat{\mathbf{W}}_k$ and $\hat{\mathbf{W}}_l$ denote the eigenvectors and $\mathbf{\Lambda}^2$ represent the diagonal matrix of eigenvalues (i.e., canonical correlations squared). The dimension of the canonical shared space is defined as the rank of covariance matrix between both multiplex feature matrices. Ultimately, each transformation matrix $\mathbf{W}_k$ is generated through sorting the eigenvectors in $\hat{\mathbf{W}}_k$ with non-zero eigenvalues. To perform paired multiplex feature fusion in the canonical space, we simply concatenate the transformed multiplex features as follows:

$$\hat{\mathbf{M}}_{k,l} = \begin{pmatrix} \hat{\mathbf{M}}_k \\ \hat{\mathbf{M}}_l \end{pmatrix} = \begin{pmatrix} \mathbf{W}_k^T\mathbf{M}_k \\ \mathbf{W}_l^T\mathbf{M}_l \end{pmatrix} = \begin{pmatrix} \mathbf{W}_k & 0 \\ 0 & \mathbf{W}_l \end{pmatrix}^T \begin{pmatrix} \mathbf{M}_k \\ \mathbf{M}_l \end{pmatrix}$$

This correlational block allows to minimise the multiplex set-specific noise and reduces multiplex data dimensionality. Since CCA works in an unsupervised manner (it is naive to the labels of subjects in the study) and does not aim to maximise the separation between the classes of patients, further classification needs to be performed using the projected features to diagnose subjects with eMCI vs. Healthy Controls. To do this, a linear support vector machine (SVM) algorithm is trained on each fused pair of training multiplex feature matrices $\hat{\mathbf{M}}_{k,l}$ to output a classification label for each subject (see fig.4.1). Noting that for each training subject, we have N multiplexes estimated, we perform C_N^2 mappings of pairs of multiplexes in $\mathbb{M}$ and train C_N^2 SVM classifiers. We chose a linear SVM for our classification task as SVMs tend to work very well in practice, even with very small training sample sizes, they are easier to optimise than more complex algorithms that can get stuck in the local minima and they do not require powerful GPUs to train, all of which makes them more applicable in practice. However, even though the diagnosis is made, the biological biomarkers of the disease are not identified as CCA does not allow for the tracking of the original features. As these limitations may restrict the applicability of the model in a clinical setting, we incorporate a discriminative block into our diagnostic framework.

Discriminative block

We simultaneously communicate the pairs of brain multiplexes to the paralleled discriminative block (see fig.4.1) where we train sets of regularized LDA classifiers using the concatenated features from different pairs in a supervised manner. LDA combines the dimensionality reduction and the classification together by attempting to maximise the difference between multiplex features so that there are distinct groups based on the given class labels. This enables LDA to find the most discriminant projection of the features. All training multiplex features are mapped into a discriminative space guided by the labels, where the discriminative paired multiplex features are generated.

Suppose we have two classes, C_1 and C_2, with n_1 samples from C_1 denoted as x_{1i} for $i = 1, 2, \ldots, n_1$, and n_2 samples from C_2 denoted as x_{2j} for $j = 1, 2, \ldots, n_2$.

1. Calculate the means: The mean of the data points was computed for each feature in each class.

Mean vector for C_1: $m_1 = \frac{1}{n_1} \sum_{i=1}^{n_1} x_{1i}$
Mean vector for C_2: $m_2 = \frac{1}{n_2} \sum_{j=1}^{n_2} x_{2j}$

2. The within-class scatter matrix (S_W) was calculated by adding the covariance matrices of each class:

$$S_W = \sum_{i=1}^{n_1} (x_{1i} - m_1)(x_{1i} - m_1)^T + \sum_{j=1}^{n_2} (x_{2j} - m_2)(x_{2j} - m_2)^T$$

3. The between-class scatter matrix (S_B) was calculated by summing up the product of transposed difference between mean of each cluster and the difference between mean of each cluster and the dot product of these with the number of data points in each class :

$$S_B = (m_1 - m_2)(m_1 - m_2)^T$$

4. Solve the generalized eigenvalue problem by dividing the between-class scatter by the within-class scatter:

$$S_W^{-1} S_B w = \lambda w$$

5. Selecting Discriminative Features:

Select the eigenvector w corresponding to the largest eigenvalue. The linear discriminant function for a sample x is given by:

$$y = w^T x$$

The sign of y can be used for classification. For example, if $y > 0$, then classify as C_1; otherwise, classify as C_2.

Diagnosis

In the testing stage, a pair of testing multiplexes will pass through the correlational block, which includes a set of P correlational classifiers, and discriminative classification blocks, which includes a set of P correlational classifiers, thereby outputting $K = 2P$ of classification labels. By aggregating the labels predicted by both blocks for all pairs of multiplexes, we obtain the final label for the target testing subject. To do so, we use majority voting by selecting the highly frequent predicted label outputted by classifiers in both blocks.

In an ensemble of K classifiers $(C_1, C_2, \ldots, C_K)$ for binary classification, the majority voting rule is applied to determine the final classification label. Let y_{final} be the final ensemble prediction.

The final classification label y_{final} is obtained by taking the majority vote:

$$y_{\text{final}} = \text{argmax}_{\{0,1\}} \sum_{i=1}^{K} \delta(y_i)$$

where:

- y_{final} is the final ensemble prediction,
- y_i is the prediction of the i-th classifier (C_i),
- $\delta(\cdot)$ is the Kronecker delta function, which returns 1 if its argument is true and 0 otherwise.

In simpler terms, the final prediction is the class label that occurs most frequently among the individual predictions of the classifiers.

By combining the data in the ensemble at the decision level to make the final diagnostic decision, we were able to overcome the limitations of the simpler linear models that make up the ensemble and make our model applicable to datasets with low sample size, which are prevalent in clinical settings.

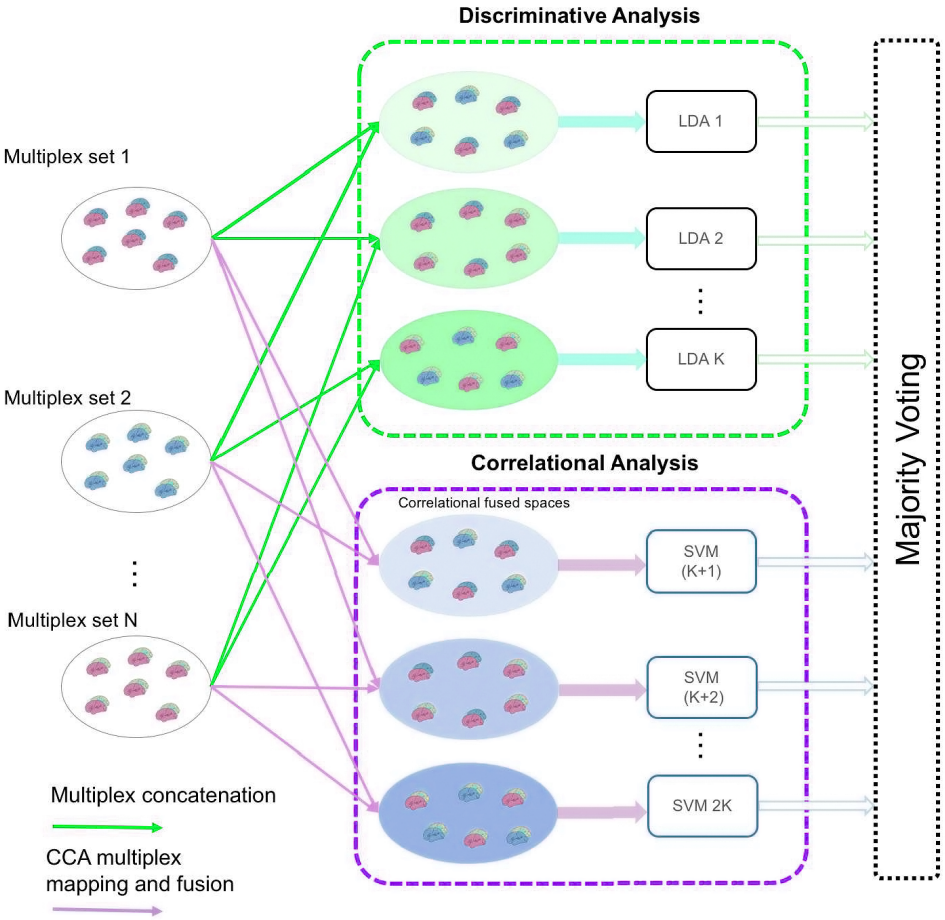


FIGURE 4.1: *The proposed machine learning pipeline. For all possible combinations of multiplex pairs, each pair of multiplexes is passed into the ensemble framework, consisting of a correlational learning block (where they are mapped by CCA and classified by SVM) and a discriminative block (where they are mapped and separated into two classes by LDA). The two blocks produce predicted class labels for the test subjects based on the analysis of subsequent pairs of multiplexes. The final class label is assigned through majority voting on labels assigned by the two blocks.* Figure adapted from [Own7]

Chapter 5

The Experiment

This chapter describes our proposed machine learning pipeline.

5.1 Experimental setup

5.1.1 Evaluation data

We evaluated the proposed classification framework using 42 eMCI (average age 70.4 ± 7.5) and 42 NC (average age 74.1 ± 6.7) age and gender-matched subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) GO public database [163], each with structural T1-w MR image [164]. The primary goal of ADNI, which was launched as a public-private partnership in 2003, is to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

We used FreeSurfer analysis suite [128, 165] to reconstruct both right and left cortical surfaces for each subject from T1-w MRI. The processing included skull stripping, motion correction, two T1-w images averaging, intensity normalization, topology correction and segmentation of the subcortical White Matter (WM) and deep Grey Matter (GM) volumetric structures to identify GM/WM and GM/Cerebrospinal fluid (CSF) boundaries, as in [166]. Then we parcellated each cortical hemisphere into 35 cortical regions using Desikan-Killiany Atlas.

5.1.2 Proposed brain multiplexes

For the convolutional brain multiplexes (CBM), we defined $N = 6$ multiplexes, each using $M = 4$ cortical network views, anchored at V1. For each cortical attribute (signal on the cortical surface), we compute the strength of the morphological network connection linking i^{th} ROI and the j^{th} ROI as the absolute difference between the averaged attribute values in both ROIs. Multiplex $\mathcal{M}_1$ includes cortical attribute views $\{\mathbf{V}_1, \mathbf{V}_2, \mathbf{V}_3, \mathbf{V}_4\}$, $\mathcal{M}_2$ includes $\{\mathbf{V}_1, \mathbf{V}_2, \mathbf{V}_4, \mathbf{V}_3\}$, $\mathcal{M}_3$ includes $\{\mathbf{V}_1, \mathbf{V}_3, \mathbf{V}_4, \mathbf{V}_2\}$, $\mathcal{M}_4$ includes $\{\mathbf{V}_1, \mathbf{V}_3, \mathbf{V}_2, \mathbf{V}_4\}$, $\mathcal{M}_5$ includes $\{\mathbf{V}_1, \mathbf{V}_4, \mathbf{V}_2, \mathbf{V}_3\}$, and $\mathcal{M}_6$ includes $\{\mathbf{V}_1, \mathbf{V}_4, \mathbf{V}_3, \mathbf{V}_2\}$.

For the proposed shallow convolutional brain multiplexes (SCBM), we define $N = C_4^2 = 6$ shallow multiplexes, by considering all possible pairings of 2 views out of 4. Multiplex $\mathcal{M}_1$ includes cortical attribute views $\{\mathbf{V}_1, \mathbf{V}_2\}$, $\mathcal{M}_2$ includes $\{\mathbf{V}_1, \mathbf{V}_3\}$, $\mathcal{M}_3$ includes $\{\mathbf{V}_1, \mathbf{V}_4\}$, $\mathcal{M}_4$ includes $\{\mathbf{V}_2, \mathbf{V}_3\}$, $\mathcal{M}_5$ includes $\{\mathbf{V}_2, \mathbf{V}_4\}$, and $\mathcal{M}_6$ includes $\{\mathbf{V}_3, \mathbf{V}_4\}$. $\mathbf{V}_1$ denotes the maximum principal curvature brain view, $\mathbf{V}_2$ denotes the mean cortical thickness brain view, $\mathbf{V}_3$ denotes the mean sulcal depth brain view, and $\mathbf{V}_4$ denotes the mean of average curvature brain view.

For our experiments, we created 4 representations of morphological brain network data: (1) 'Views' by concatenating all morphological brain networks, (2) 'Correlational multiplexes' with inter-layer computed using Pearson correlation, (3) 'Convolutional multiplexes' composed of 4 intra-layers with inter-layers generated using 2D convolution, and (4) 'Shallow convolutional multiplexes' composed of 2 intra-layers with inter-layers generated using 2D convolution.

Remark 1: The morphological networks and multiplexes are constructed separately for the left and the right hemispheres and they are studied independently, as we do not want our morphological connections to be 'biased' by brain hemispheric asymmetry. It also prevents the loss of insightful information on how eMCI affects each hemisphere independently.

Remark 2: In the convolutional brain multiplexes, the convolution operation between intra-layers captures the signal within a subgraph (a small patch in the connectivity matrix) extracted from a first layer (whole matrix) as an expression of other subgraphs extracted from a second layer. One can think of the inter-layer network as a 'high-order blending' of both intra-layers, expressing the amount of overlap of intra-layer 1 as it is shifted over intra-layer 2.

5.1.3 Comparison methods

To demonstrate the effectiveness of integrating correlational and discriminative methods into a single framework, we benchmarked our method against several discriminative methods including Eigenvector Centrality (ECFS) [167], Mutual Information (MutInf-FS) [168], and Infinite Feature Selection (Inf-FS) [148]. We also benchmarked our method against the correlational CCA-based eMCI/NC classification framework in [Own4]. We also evaluated the performance of each of the above discriminative methods when combined with CCA using our proposed framework. Additionally, we benchmarked against newer discriminative and correlational methods, Tensor CCA (TCCA) [156], the multi-view Discriminant Analysis (MvDA) [169], and finally the two methods combined into a paired classifier.

The first method, Tensor CCA (TCCA) [156], utilizes tensors for a correlation analysis of an arbitrary number of views. Specifically, TCCA maps multiple views into covariance tensors where correlated features can be identified, maximizing the correlation between several views and hence improving upon traditional CCA methods which are optimized for pair-wise correlation. Furthermore, TCCA is capable of identifying high-order correlation information by also adopting the alternating least squares (ALS) algorithm, further improving upon its correlational counterparts. The second method, Multi-view Discriminant Analysis (MvDA) [169], follows a similar process by extending traditional LDA to support multiple views. MvDA aims to maximize the between-class variations while simultaneously minimizing any within-class variance, consequently highlighting discriminative features. Subsequently, we combine both MvDA and TCCA into a single framework for a final benchmark, to allow for the analysis of the shared information between the correlational and discriminative methods.

5.1.4 Experimental setup

To make the best use of our small dataset, we used leave-one-out cross-validation (LOO) to evaluate our proposed method and its comparison methods. We train the model on the data with the number of subjects minus one and subsequently predict a label for the subject that was left out in the training phase. This process is repeated until there are predicted labels for every subject where they can be compared to the ground truth labels. Since we have a balanced dataset across the two classes, we can use the metric of accuracy to evaluate the performance of our classification model.

Accuracy is defined as the ratio of correctly predicted instances to the total number of instances. The formula for accuracy is as follows:

$$\text{Accuracy} = \frac{\text{Number of Correct Predictions}}{\text{Total Number of Predictions}}$$

In mathematical terms:

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN}$$

where:

- TP (True Positives) is the number of instances correctly predicted as positive.
- TN (True Negatives) is the number of instances correctly predicted as negative.
- FP (False Positives) is the number of instances incorrectly predicted as positive.
- FN (False Negatives) is the number of instances incorrectly predicted as negative.

We also calculate the model's **Sensitivity (True Positive Rate or Recall):**

$$\text{Sensitivity} = \frac{\text{True Positives (TP)}}{\text{True Positives (TP)} + \text{False Negatives (FN)}}$$

and **Specificity (True Negative Rate):**

$$\text{Specificity} = \frac{\text{True Negatives (TN)}}{\text{True Negatives (TN)} + \text{False Positives (FP)}}$$

These metrics provide valuable insights into the performance of a binary classification model, particularly in situations where the costs of false positives and false negatives are different.

In the correlational block, we keep the parameter C (strength of penalty imposed on misclassified data by the SVM) set at default $C = 1$, which aids the training efficiently, while avoiding overfitting of the model to the training data. Furthermore, due to MvDA containing an optimization variable, λ, we tuned it using inner 5-fold cross-validation, starting with $\lambda = 0.1$ and iterating through to 0.9 with a step size of 0.1. This form of nested cross-validation was used for two other variables in the experiment. Since, the performance of the model heavily depends on the number of input features, the number of selected features for ECFS and MutInfFS was automatically tuned using the nested 5-fold cross-validation technique, where the feature size varied from 50 to 400 with a step size of 50. Additionally, since exhaustive hyper-parameter tuning is not feasible for the TCCA method due to the cumbersome runtime of the method, we empirically tuned specific variables in TCCA. To do this, we set the optimization variable ϵ to 0.5 and tuned the number of features for each data type. Finally, ECFS, TCCA, and MvDA required dimensionality reduction on high-dimensional data, due to computational limitations and memory overload. Consequently, PCA was applied to the data for dimensionality reduction. For the ECFS method, we applied PCA to the deep convolutional multiplexes as it was unable to handle high dimensional data. According to [159], the PCA might aid in improving the classification performance of early demented patients from healthy controls using morphological brain features.

Fig.5.2 displays the accuracy, sensitivity, and specificity for each method. Each benchmark method shows results for morphological views, correlational multiplexes [129], convolutional multiplexes [Own4], and shallow convolutional multiplexes in both hemispheres. Additionally, in fig.5.1, we show the comparison between independent LDA, CCA, and our proposed method, showing the accuracy for each data type.

5.1.5 Identification of the most discriminative features

To identify the top 10 most discriminative features from each morphological view, we applied ECFS which returned a ranking of features, from the most to the least discriminative. We decided to use ECFS as, unlike LDA which projects features onto a new more discriminative space, enables tracking of the original morphological features, and retains the biological interpretability of the results. Further, ECFS appeared to be the second-best performing discriminative method after LDA. The ranking of features was averaged between all subjects to produce circular graphs showing features (in this case morphological connections) that were consistently identified as most discriminative for each view fig.5.4. Fig.5.3 contains the visualized brain regions referred to by the circular graphs together with their corresponding names.

Weights were then produced for each feature where they were correlated with the thickness of the edge in the circular graph. The most highly correlated features are not shown due to neither TCCA nor CCA returning a ranking of features but directly projecting the data within their methods, which inhibits tracking of the original features.

5.2 Results

The best accuracy was always obtained using the proposed framework with shallow convolutional multiplexes for the right hemisphere, with an accuracy of 80.95% (see fig.5.1). The proposed framework improved upon the independent methods, increasing the accuracy by 3-7% in the right hemisphere. The left hemisphere results show a contrasting conclusion, achieving the best accuracy at 76.19% using independent LDA with correlational multiplexes (as demonstrated in fig.5.1). This difference in model performance between the two hemispheres might be explained by the way early dementia biomarkers manifest in the data, with some biomarkers being more difficult to identify by different machine learning methods.

From the circular graphs that identify the top 10 most discriminative connections (fig.5.4), several compelling observations can be made. The most noticeable of which is the significance of the entorhinal cortex, which participates in almost every connection in both hemispheres in all views. It appears to serve as a hub region, interconnecting other brain regions and can serve as a significant biomarker in identifying early stages of dementia. The brain regions connected to the entorhinal cortex would consequently get affected by the disease, especially where strong connections are identified. For example, the connection from the entorhinal cortex to the insula cortex appears in the maximum principal curvature and the mean sulcal depth view in both hemispheres and in the mean average curvature view in the left hemisphere. Another prominent connection joins the entorhinal cortex with the rostral anterior cingulate cortex in the maximum principal curvature and the mean average curvature view in both hemispheres and in the mean sulcal depth view in the left hemisphere. Further, the connection to the isthmus-cingulate cortex was observed in the maximum principal curvature, the mean cortical thickness and the mean sulcal depth views for both hemispheres. This may be due to the proximity of these three brain regions to the entorhinal cortex, causing them to be affected by early stages of dementia. Interestingly,

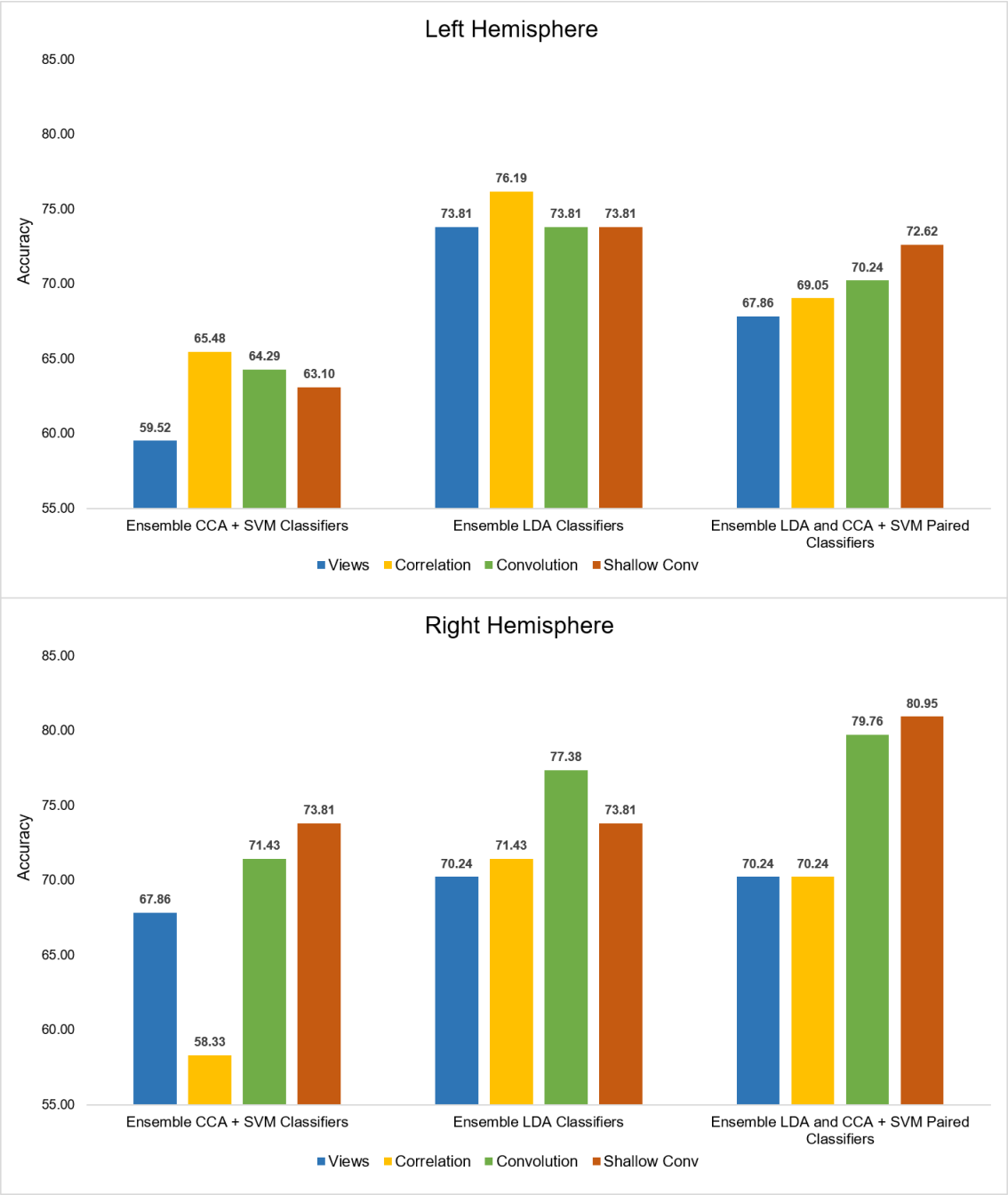


FIGURE 5.1: *Classification accuracy for all data types in both the left and right hemispheres. Shown are the proposed method, Ensemble LDA and CCA-SVM Paired Classifiers, and its constituent methods Ensemble SVM Paired Classifiers using CCA and Ensemble LDA Paired Classifiers.* Views: morphological brain views. Correlation: correlational brain multiplexes. Convolution: Convolutional brain multiplexes. Shallow Conv: proposed shallow convolutional multiplex.

consistent connections from the entorhinal cortex to further brain regions were also noted. The connection to the pericalcarine cortex was present for both hemispheres in all views indicating that it may be a good biomarker for early dementia identification. Another connection involved the posterior-cingulate cortex and was present for both hemispheres in the maximum principal curvature and the mean average curvature view and for the right hemisphere in the mean sulcal depth view. In contrast, a strong connection that does not involve the entorhinal cortex region connects the parahippocampal gyrus and the transverse temporal cortex and is only present in the

		Left Hemisphere			Right Hemisphere		
Method	Dataset	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
Ensemble SVM Paired Classifiers using CCA	Views	59.52	52.38	66.67	67.86	61.9	73.81
	Correlational	65.48	69.05	61.9	58.33	64.29	52.38
	Convolutional	64.29	66.67	61.9	71.43	73.81	69.05
	Shallow Conv	63.1	66.67	59.52	73.81	76.19	71.43
Ensemble SVM Paired Classifiers using ECFS	Views	58.33	50	66.67	73.81	64.29	83.33
	Correlational	65.29	61.9	66.67	73.81	73.81	73.81
	Convolutional	63.1	64.29	61.9	76.19	73.81	78.57
	Shallow Conv	70.24	76.19	64.29	66.67	66.67	66.67
Ensemble SVM Paired Classifiers using CCA + ECFS	Views	59.52	52.38	66.67	69.05	64.29	73.81
	Correlational	53.57	57.14	50	57.14	61.9	52.38
	Convolutional	57.14	59.52	54.76	70.24	73.81	66.67
	Shallow Conv	63.1	66.67	59.52	78.57	78.57	78.57
Ensemble SVM Paired Classifiers using MutInf-FS	Views	61.9	50	73.81	72.62	66.67	78.57
	Correlational	55.59	52.38	59.52	63.1	61.9	64.29
	Convolutional	57.14	57.14	57.14	64.29	64.29	64.29
	Shallow Conv	66.67	71.43	61.9	76.19	78.57	73.81
Ensemble SVM Paired Classifiers using CCA + MutInf-FS	Views	64.29	59.52	69.05	66.67	61.9	71.43
	Correlational	64.29	69.05	59.52	54.76	57.14	52.38
	Convolutional	58.33	61.9	54.76	71.43	71.43	71.43
	Shallow Conv	63.09	69.05	57.14	77.38	78.57	76.19
SVM Classifier using MvDA	Views	66.67	66.67	66.67	78.57	85.71	71.43
	Correlational	66.67	66.67	66.67	72.62	71.43	73.81
	Convolutional	69.05	71.43	66.67	76.19	73.81	78.57
	Shallow Conv	69.05	69.05	69.05	78.57	78.57	78.57
Ensemble SVM Paired Classifiers using TCCA	Views	71.43	66.67	76.19	75	71.43	78.57
	Correlational	71.43	76.19	66.67	66.6	69.05	64.29
	Convolutional	69.05	69.05	69.05	70.24	69.05	71.43
	Shallow Conv	69.05	73.91	64.29	75	78.57	71.43
Ensemble SVM Paired Classifiers using MvDA + TCCA	Views	71.43	73.81	69.05	75	90.45	59.52
	Correlational	70.24	85.71	54.76	66.67	69.05	64.29
	Convolutional	70.24	69.05	71.43	73.81	88.1	59.52
	Shallow Conv	72.62	73.81	71.43	77.38	69.05	85.71
Ensemble LDA Paired Classifiers	Views	73.81	76.19	71.43	70.24	61.9	78.57
	Correlational	**76.19**	**78.57**	**73.81**	71.43	71.43	71.43
	Convolutional	73.81	78.57	69.05	77.38	78.57	76.19
	Shallow Conv	73.81	80.95	66.67	73.81	73.81	73.81
Ensemble LDA and CCA-SVM Paired Classifiers **(Ours)**	Views	67.86	76.19	59.52	70.24	69.05	71.43
	Correlational	69.05	66.67	71.43	70.24	66.67	73.81
	Convolutional	70.24	73.81	66.67	**79.76**	**78.57**	**80.95**
	Shallow Conv	72.62	78.57	66.67	**80.95**	**83.33**	**78.57**

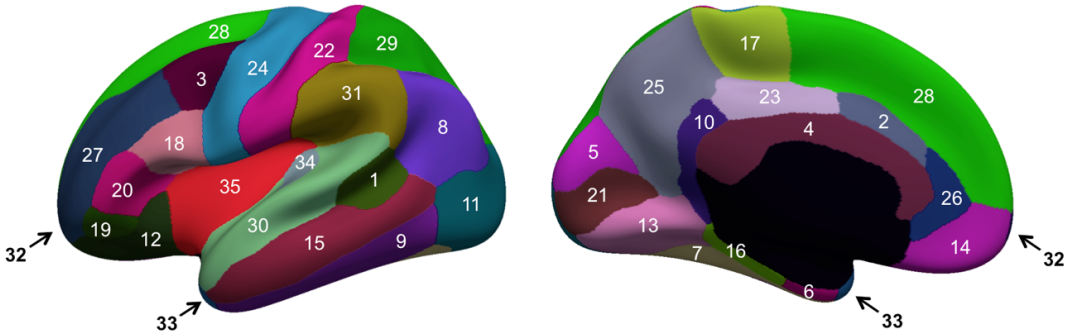
FIGURE 5.2: *Average eMCI/NC classification accuracy using our method and different comparison methods.* Views: morphological brain views. Correlation: correlational brain multiplexes. Convolution: Convolutional brain multiplexes. Shallow Conv: proposed shallow convolutional multiplex.

mean sulcal depth view in the right hemisphere.

5.3 Discussion

5.3.1 Performance of the proposed method

We proposed a novel machine learning framework that pairs discriminative and correlational methods in an ensemble to leverage the complementary information for early dementia diagnosis that



1. Bank of the Superior Temporal Sulcus	**2.** Caudal Anterior-cingulate Cortex
3. Caudal Middle Frontal Gyrus	**4.** Unmeasured Corpus Callosum
5. Cuneus Cortex	**6.** Entorhinal Cortex
7. Fusiform Gyrus	**8.** Inferior Parietal Cortex
9. Inferior Temporal Gyrus	**10.** Isthmus-cingulate Cortex
11. Lateral occipital cortex	**12.** Lateral orbital frontal cortex
13. Lingual gyrus	**14.** Medial orbital frontal cortex
15. Middle temporal gyrus	**16.** Parahippocampal gyrus
17. Paracentral lobule	**18.** Pars opercularis
19. Pars orbitalis	**20.** Pars triangularis
21. Pericalcarine cortex	**22.** Postcentral gyrus
23. Posterior-cingulate cortex	**24.** Precentral gyrus
25. Precuneus cortex	**26.** Rostral anterior cingulate cortex
27. Rostral middle frontal gyrus	**28.** Superior frontal gyrus
29. Superior parietal cortex	**30.** Superior temporal gyrus
31. Supramarginal gyrus	**32.** Frontal pole
33. Temporal pole	**34.** Transverse temporal cortex
35. Insula cortex	

FIGURE 5.3: *Cortical brain regions used for network construction with their corresponding names.*

can otherwise be neglected when using these approaches in separation. We also introduced a novel morphological brain multiplex structure, consisting of 2 layers of morphological brain networks and 1 layer computing the relationship between them. This way we improved upon the deep convolutional multiplex structure from our previous research [Own4] by reducing the data dimensionality and redundancy of features across the individual classifiers in the ensemble.

As demonstrated in fig.5.1 our proposed framework significantly outperformed several comparison methods when focusing on both the deep and shallow brain multiplexes in the right hemisphere. In this case, the combination of discriminative LDA and correlational CCA methods led to a large increase in diagnostic performance over either of the independent methods alone. A similar trend was observed across different combinations of discriminative and correlational methods in the right hemisphere. For example, both ECFS and MutInf-FS improved their accuracy when paired with CCA for the shallow multiplex data yielding their highest performance, further demonstrating the proposed framework's improvement.

Contrasting results were observed for the data from the left hemisphere. The independent discriminative LDA achieved the best accuracy using correlational multiplexes. These opposing results might indicate that early stages of dementia affect the hemispheres in different ways. The

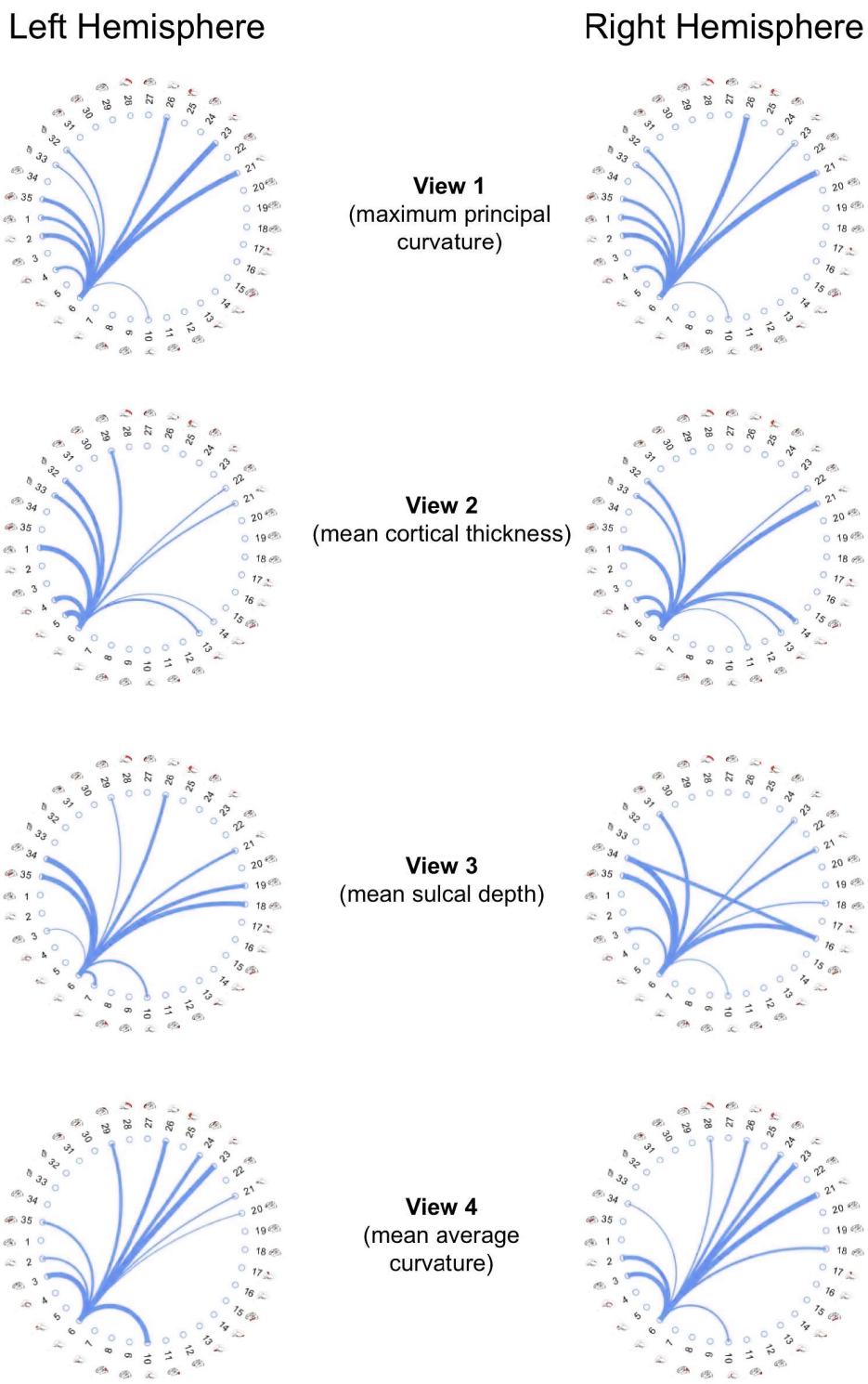


FIGURE 5.4: *Circular graphs displaying the top 10 most discriminative features and the corresponding regions of the brain identified by ECFS. Each view denotes a certain feature: View 1 shows the maximum principal curvature; View 2 shows the mean cortical thickness; View 3 shows the mean sulcal depth; and View 4 shows the mean average curvature.*

benchmark methods maintained a consistent performance with the proposed framework with the model accuracy notably lower for the left hemisphere (fig.5.2).

5.3.2 Performance on the right and the left hemisphere

There is a visible disparity in the diagnostic performance of the researched methods between the right and the left hemisphere. Training different models on the right hemisphere results in a relatively good accuracy across both discriminative and correlational methods contributing to a good performance of the proposed combined method. Indeed, the proposed model outperformed a correlational CCA-based ensemble classifier introduced in [Own4]. In contrast, the accuracy on the left hemisphere is generally lower with the exception of the discriminative LDA algorithm. Despite the good performance of the proposed algorithm on the right hemisphere, pairing the discriminative methods with CCA is detrimental to the model performance for the left hemisphere compared to standalone discriminative methods. This issue can be explained by the consistent underperformance of the correlational CCA method on the left hemisphere as compared to the right, with a 10% decrease in accuracy between the hemispheres (fig.5.2). Interestingly, CCA fusion method was shown to underperform on the left hemisphere in the early dementia diagnosis task in our previous research [Own4], while performing well on the right hemisphere ((fig.5.5)). The performance was improved significantly when structure information was added in the feature mapping step by applying a structured sparse CCA (SS-CCA) instead [Own5]. This implies that the structure information is important when diagnosing early dementia progression in the left hemisphere and could bring complementary information to our pipeline when paired with the discriminative methods. Indeed, as shown in our previous research [Own5], to obtain a superior performance of the ensemble algorithm, each individual classifier that constitutes it, needs to perform well above a chance to have a positive impact on the accuracy of the whole system. When the difference in accuracy between the correlational and discriminative methods is small, combining these methods in an ensemble results in an improved overall performance (fig.5.2). However, when one of the methods underperforms in comparison to the other, the accuracy of their ensemble tends to average between the accuracy of the two constituent methods. This is caused by the majority voting that combines the predictions from the individual classifiers being biased by the underperforming algorithm to assign incorrect labels to make the final diagnostic decision.

5.3.3 Analysis of early dementia biomarkers

Using the discriminative feature selection ECFS to identify the most discriminative features for each morphological view, we were able to identify the most significant biomarkers for displaying early signs of dementia. One of the most notable findings was the prominence of the entorhinal cortex which participated in almost all identified morphological connections in both hemispheres across all views. Entorhinal cortex was also found to be an important hub region for early dementia diagnosis in our previous research [Own5], where a correlational feature mapping SS-CCA was used on pairs of morphological brain views to identify features that were highly correlated between different cortical attributes. Further to being responsible for many connections to different brain regions, entorhinal cortex plays an important role in navigation and formation and consolidation of spatial and declarative memory and has been shown to be one of the first brain regions to be affected by early states of dementia [170, 171]. Various research has shown that the pathological changes in the neuronal structure and function of the entorhinal cortex occur before the onset of any AD symptoms [172], making it a crucial biomarker for early dementia diagnosis when the medical intervention may delay the onset of symptoms.

The connections that consistently appeared for both hemispheres across different morphological views were connecting the entorhinal cortex and the pericalcarine cortex and connecting the entorhinal cortex and the insula cortex, consistent with our results when using correlational

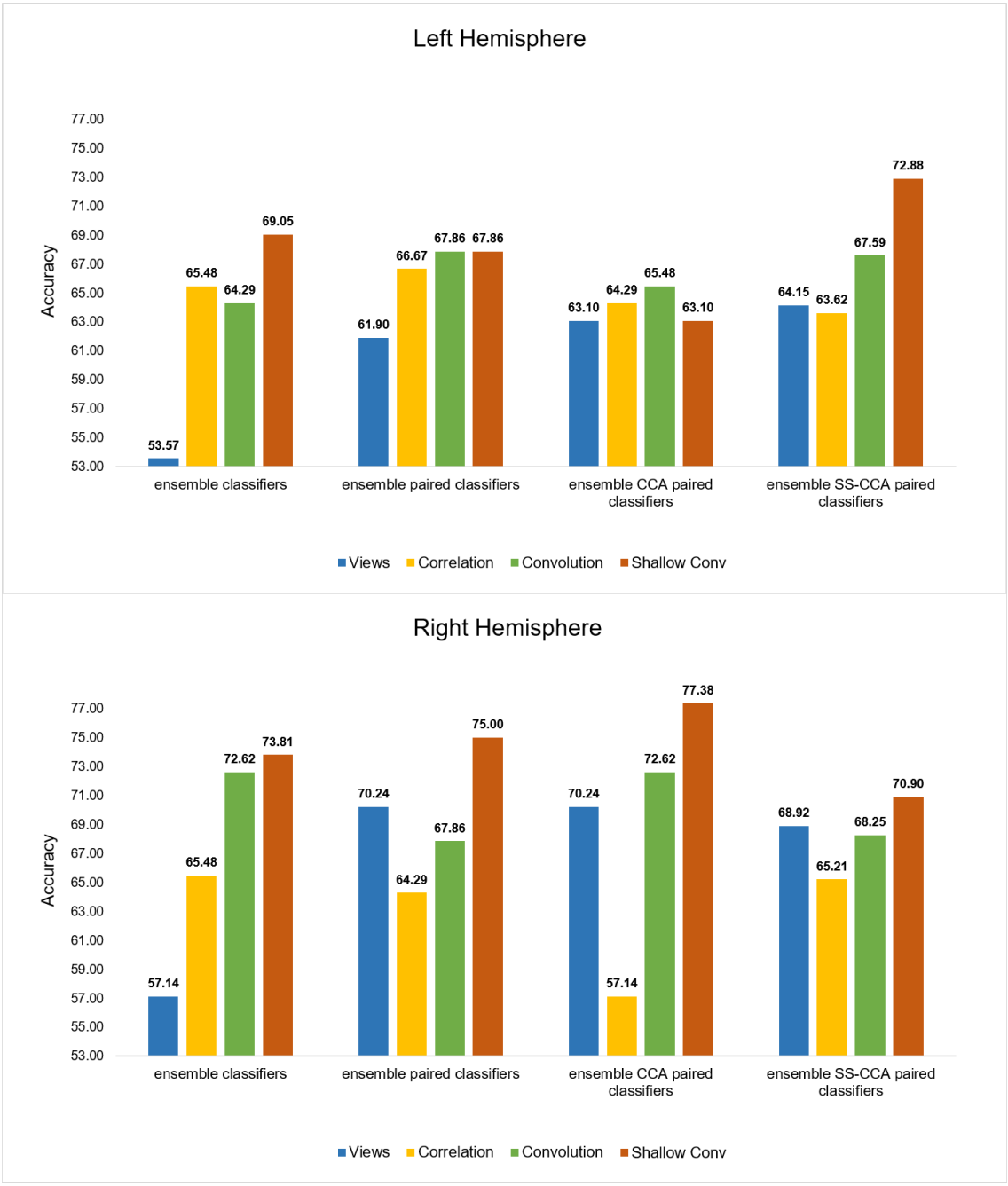


FIGURE 5.5: *Classification accuracies for the joint pairing and structured GGL-SCCA mapping of brain features comparison with other ensemble classifier methods.* Views: morphological brain views. Correlation: correlational brain multiplexes. Convolution: Convolutional brain multiplexes. Shallow Conv: proposed shallow convolutional multiplex. Figure adapted from [Own5]

methods [Own5]. Indeed, using the structure information within the CCA mapping revealed the pericalcarine cortex as a hub region in the left hemisphere and the insula cortex as a hub region in both hemispheres. The insula cortex is involved in the integration of multimodal inputs, interoceptive awareness, processing and regulation of emotions, and social cognition [173]. In patients with AD the reduction in the insular volume was associated with the occurrence of neuropsychiatric symptoms, such as agitation and apathy [174]. Other studies showed that disrupted connectivity between the insula and other brain regions involved in cognitive and social processing was associated with cognitive impairment in AD [175, 176]. Pericalcarine cortex is located in the occipital

lobe and its main function is to process visual information, specifically information related to the perception of spatial orientation, colour, and form. It is also involved in the processing of visual motion and depth perception [177]. Information from the pericalcarine cortex is sent to other regions of the brain, where it is integrated with other sensory information to form a complete perception of the environment. Previous research has shown that damage to the pericalcarine cortex can lead to visual deficits such as difficulty with object recognition, spatial navigation, and visual perception in patients with AD [178]. In addition to visual deficits, damage to the pericalcarine cortex and its connections to other brain regions can also result in disruptions to the sleep-wake cycle and circadian rhythm, which are common in individuals with dementia [179]. It has been shown that hypometabolism in the pericalcarine cortex was a characteristic feature of Alzheimer's disease and that this deficit was already present even in the early stages of the disease, such as MCI which may convert into AD, making it a promising biomarker for early disease diagnosis [178,180].

These brain regions are possible next targets for early dementia likely progressing from the entorhinal cortex and reaching out through the proximal highly connected hub nodes onto other connected brain regions. Interestingly, when looking at the cortical thickness brain view, similar brain regions were identified as important early dementia biomarkers in both our studies, using discriminative feature selection ECFS method and correlational feature mapping SS-CCA [Own5, Own7]. These included connections concentrating around the Frontal pole, the Temporal pole, the Insula cortex, the Bank of Superior Temporal Sulcus, the Corpus Callosum, and the Entorhinal cortex, with these likely being affected in early dementia. Additionally, it was observed that the most prominent identified features remained consistent across all the morphological brain views, which might indicate that dementia affects at least some of the morphological connections uniformly.

Interestingly, one odd connection that was only present in the mean sulcal depth view in the right hemisphere was reaching between the parahippocampal gyrus and the transverse temporal cortex, two neighbouring regions in the brain that are functionally and structurally connected. The transverse temporal cortex was previously identified as a hub region when using the SS-CCA mapping [Own5] with a significant connection reaching to another hub region, the pericalcarine cortex. The transverse temporal cortex is involved in the processing of auditory information, including the perception of speech (language), music, and other sounds [181]. Studies that analysed structural changes in AD have shown that reduced gray matter volume and white matter connectivity in the transverse temporal cortex were associated with cognitive impairment, including language impairment in individuals with AD and its precursor - MCI [182, 183]. The parahippocampal gyrus plays a crucial role in memory processing and storage and takes part in the integration of visual and spatial information [184,185]. A dysfunction in this brain region may contribute to the cognitive deficits seen in Alzheimer's disease and other types of dementia [186]. [187] and [188] showed that reduced gray matter volume and cortical thickness in the parahippocampal gyrus were associated with cognitive decline in AD, while [180] showed that gray matter volume and glucose metabolism were already present in patients with MCI. Recent studies using neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) have shown that there is a strong connection between the transverse temporal cortex and the parahippocampal gyrus. Specifically, the transverse temporal cortex sends auditory information to the parahippocampal gyrus, which is important for the encoding and retrieval of auditory memories [189,190]. We identify the morphological connection between the parahippocampal gyrus and the transverse temporal cortex as an important biomarker for early dementia identification. Together with the above findings, our algorithm may assist in identifying early stages of dementia by clearly displaying significant biomarkers and patterns in brain scans of the affected patients

and prompt early intervention.

5.3.4 Novel multiplex structure

In our previous research, we demonstrated that the ensemble classifier, which combines the prediction scores from multiple base classifiers using convolutional multiplexes, is more effective at distinguishing between eMCI patients and NC than any of the individual classifiers used independently for both the left and right hemisphere [Own5]. This suggests that different multiplexes, composed of various morphological brain networks and a unique relationship between them, provide complementary information for early dementia diagnosis.

We also showed that incorporating the information about the relationships between different cortical networks, by computing convolutional interlayers and integrating them into a multiplex structure, led to improved accuracy in diagnosing dementia in its early stages compared to using different brain networks alone (as shown in fig.5.1) [Own5]. This suggests that understanding how eMCI affects one cortical attribute in relation to another can provide valuable insight into the mechanisms of the disease onset. Additionally, our proposed shallow multiplex structure, exploring the relationship between 2 different morphological networks was designed to address the limitations of the ensemble learning, which used convolutional multiplexes containing all the morphological brain views. For the overall ensemble to be more accurate than its individual members, the classifiers in the ensemble must be discriminative (they should perform better than what could be achieved by random guessing) and diverse (each of the base classifiers in the ensemble should be uncorrelated with the rest), ensuring that each classifier makes different errors on test data [135]. However, different deep convolutional multiplexes contain overlapping features, resulting in highly correlated input data that can lead to suboptimal ensemble performance. Our new shallow multiplex structure [Own5, Own6, Own7] reduced the correlation between individual classifiers in the ensemble, resulting in a better diagnostic performance compared to the deep convolutional multiplex structure (as shown in fig.5.1) and consistently outperformed other methods, such as concatenated MBN views and correlational brain multiplexes, in the right hemisphere, with the exception of independent ECFS [Own7].

5.3.5 Limitations and future work

In this work, we leveraged the strengths of ensemble learning that incorporates correlational feature fusion and discriminative feature selection methods in the base classifiers. In order to improve the proposed classification algorithm, it is crucial to tackle the limitations detected during the assessment of the outcomes acquired from our experiment. One possible future direction would be to incorporate more complex base algorithms in the ensemble. As data and computational power become more readily available, we can use more advanced machine learning classifiers like random forests and neural networks as the base classifiers to enhance the accuracy of early dementia classification through ensembles. However, using linear classifiers as individual classifiers in the ensemble has the advantage of producing consistent results that are not significantly affected by minor changes in the training data [135]. Conversely, [125] conducted a study to investigate how different classifiers affected the performance of MCI/NC classification using morphological brain features. They found that various classifiers achieved comparable results when using the same modalities and features, indicating that the selection of neuroimaging features may be more crucial than the choice of the learning algorithm in early dementia diagnosis. Since our algorithm is designed to work well on limited data and requires a feasible amount of computational power to be applicable in a real-life clinical setting, the next steps in improving the algorithm performance

should focus on adjusting the voting strategy of the ensemble learning algorithm and improving the feature fusion/selection methods used in the base classifiers.

In particular, the main limitation of the study is the performance of the proposed framework and comparison methods in the left hemisphere. Both correlational and discriminative methods exhibit a significant performance gap between hemispheres, with the right hemisphere consistently producing better results. The CCA method used for benchmarking performs particularly poorly in the left hemisphere and negatively affects the paired method's performance. Identifying features in the left hemisphere may be more difficult, as dementia may present itself differently in each hemisphere. Furthermore, the discriminative methods, ECFS and MutInf-FS, experience a significant drop in accuracy when applied to the left hemisphere. In this situation, it may be more suitable to adjust the voting strategy of the ensemble to produce the final diagnostic decision. In our experiment, all base classifiers are given equal weight when deciding the outcome label, which results in poor-performing base classifiers reducing the overall accuracy of the ensemble. By assessing the performance of the individual base algorithms, we could give higher weights to the classifiers that use more informative features and produce more accurate diagnoses to improve the final decision.

Furthermore, since the left hemisphere seems to be more sensitive to the feature selection methods used, finding correlational and discriminative methods that improve the results of the ensemble for the left hemisphere would be the next step in our future work. In our previous research [Own5], we showed that incorporating the structure information into the feature mapping step by applying SS-CCA produces significantly better results for the left hemisphere than simple CCA or any other feature fusion and selection methods used in this work [Own7]. This shows that the combination of features used may be more informative for dementia diagnosis in the left hemisphere than the individual features alone. It would be interesting to see how well incorporating SS-CCA into our framework would perform. Further, we could go beyond correlational methods that assume linear relationships between variables, such as CCA, SS-CCA, or TCCA. For example, Deep CCA which learns complex non-linear transformations of two views through deep networks was shown to find higher correlations than those learned by CCA and kernel CCA [191]. Also, enhancing the discriminative methods could greatly improve the overall accuracy of the results. Introducing more effective feature selection techniques that rank features, such as ECFS [167] and MutInf-FS [168], could be beneficial. A more accurate method would be able to identify more biomarkers within the left hemisphere, leading to a better understanding of the disease and improved accuracy in classification.

Our study demonstrated the significance of the relationship between various cortical brain networks in improving early dementia diagnosis. However, we were unable to identify the most informative brain connection relationships between different networks due to the necessity to apply a dimensionality reduction method before the feature mapping/selection. On top of that, we observed inconsistent performance of the newly proposed methods TCCA, MvDA, and their paired classifier. These methods obtained good individual accuracy, but their performance was weakened when paired. A potential reason for this outcome would be the need to apply PCA to the input data as neither of the methods is capable of handling high-dimensional data directly. PCA has been shown to improve classification accuracy by reducing redundancy, as shown in our research [Own5], but it can also remove valuable features, thereby affecting performance in either direction [159, 192]. This effect of PCA can also be observed in the fluctuations of ECFS performance when using convolutional data. To address these issues, future research should explore alternative feature mapping and selection methods that are less sensitive to high-dimensional data or alternative feature mapping and selection techniques that do not compromise the interpretability

of the projected features.

Finally, in addition to investigating how dementia affects the relationship between connections from different cortical networks, a particularly exciting advancement would be to understand how the underlying structural and functional networks are influenced in relation to the changes in brain morphology that occur in early dementia. This would involve examining how the neuronal connections and their function are affected when there are observed changes in brain shape. According to the tension theory of cerebral cortex morphogenesis, changes in the morphological properties of the cortex, which are linked to cortical folding, correspond to changes in the underlying neuronal connectivity [121]. Therefore, we anticipate that by jointly exploring changes in brain morphological, structural, and functional networks, we could further enhance the classification accuracy of our model for more dependable early dementia diagnosis. By analysing how the structural and functional networks change in relation to the morphological networks we could also prove further the validity of using the information about the morphological brain structure acquired from structural MRI for early MCI diagnosis in a clinical setting.

Conclusion

In Chapter 1 we discussed how the aging World population and the growing complexity of health problems it experiences puts increasing pressure on the hospital-centric healthcare system. We also described the recent developments in healthcare, with digitalisation of the medical records opening new possibilities for data analysis leading to a more evidence-based approach to diagnosis and patient care. We also discussed some of the limitations of the existing approaches that need to be addressed on the way to a value-based future of healthcare.

In Chapter 2 we introduced machine learning and described how it is able to overcome the limitations of the traditional predictive methods in supporting the implementation of precision medicine in clinics. We also looked at several potential examples of machine learning applications in medicine, while also bringing attention to the challenges that still need to be addressed before AI can be widely implemented in a clinical setting. In summary, for a machine learning model to realistically be able to support healthcare professionals with making diagnostic decisions as part of their daily routine, the model needs to satisfy the following criteria:

- **Goal 1** Achieve diagnostic performance that is better than current state-of-the-art solutions, and at least as good as a medical professional.
- **Goal 2** Work on small highly complex data that can be realistically obtained in clinics using low-cost non-invasive procedures.
- **Goal 3** Be sensitive to very slight deviations from the norm that are present far before the appearance of any symptoms to help identify patients who are actionable for preventative interventions.
- **Goal 4** Bring complementary information together from a variety of sources to obtain a more complete picture of the individual's health and enable a more personalised approach to the delivery of treatment recommendations.
- **Goal 5** Be transparent in how it reached the diagnostic decision by preserving the interpretability of features that were deemed important by the algorithm in producing the outcome.
- **Goal 6** Derive new insight into the mechanism of the disease by identifying important biological biomarkers that could not be spotted by the human observer.

As described in the **2.8 Purpose and contribution of the project** on page 16 the aim of this project was to develop an idea of a machine learning solution that would deliver an automated diagnosis, focusing on early dementia, and could in the future be realistically applied in clinical practice by striving to satisfy as many of the above conditions as possible. To satisfy **Goal 3** we decided to focus on the diagnosis of early stages of dementia as it is a particularly challenging task for both human clinicians and AI-assisted technology. Despite much success in AI-driven diagnosis

of various conditions, AI application in psychiatric disorders diagnosis remains limited due to a number of considerations that our algorithm had to account for.

Problem In Chapter 3 we described the unique challenges of machine learning applications on brain data and discussed the current advances in research that applied machine learning to connectomic data to diagnose dementia. We noted that most current approaches relied on using data from functional or diffusion-based MRI, which are difficult to acquire as they are costly, time-consuming, and prone to noise. Further to that, most existing research working on dementia diagnosis did not focus on the very early stages of dementia before the appearance of the symptoms.

Solution We built our solution for very early dementia diagnosis by making use of the tension theory of cerebral cortex morphogenesis, according to which changes in the morphological attributes on the surface of the brain reflect the underlying changes in the structural and functional connectivity. Since the morphology of the brain surface can be studied based on T1-weighted MRI images, which are much less costly and time-consuming to acquire than the other forms of brain imaging, it makes it more applicable in clinical routine and satisfied **Goal 2** of our machine learning model. Therefore, in section **3.4.1 Morphological network construction** on page 26 we introduced a new form of brain data that can be used as an input to a diagnostic pipeline while avoiding costly screening of patients called the Morphological Brain Network. Furthermore, to satisfy **Goal 6** and to make the best use of available data, in **3.4.3 Multi-layer Networks – Introducing Multiplex Structure** on page 27 we also introduced a novel data structure called Brain Multiplex that brings further important information into the system, which could be valuable in making a correct diagnosis and contribute to a better understanding of the disease progression.

Problem In Chapter 4 we discussed possible approaches to combining data from multiple modalities in a machine learning pipeline to produce the diagnostic decision. We specifically talked about the feature level fusion methods, encompassing discriminative methods and correlational methods and decision level fusion methods like ensembles. We noted that existing research, including our previous solutions described in section **4.3.3 Previous works** on page 35 used either of these methods in isolation, which may lead to missing complementary information that could be useful for making a correct diagnostic decision.

Solution in section **4.3.4 Newest Contribution** on page 35 we introduced our proposed machine learning pipeline that addresses these limitations by combining feature fusion methods from two different families: correlational methods and discriminative methods into one ensemble model. This way, we were able to design a model capable of combining data from multiple sources in a way that maximises the relevant information and minimises the noise to make the best use of the limited data available and achieve **Goal 4** of the diagnostic model.

In Chapter 5 we detailed the experimental setup for testing our framework on data from patients with early mild cognitive impairment and healthy controls to evaluate our framework's capacity to diagnose Alzheimer's Disease at the very early stages. In section **5.2 Results** on page 44 we demonstrate that our system is sensitive to small changes in patients' brain morphology and outperforms the state-of-the-art solutions on the ADNI GO dataset, meeting our model's **Goal 1** and **Goal 3**. Further, **Goal 5** and **Goal 6** were met thanks to the preserved interpretability of the features in the discriminative block of our proposed framework when using the ECFS feature selection method. This way we were able to derive new insights into the mechanism of Alzheimer's Disease progression across the brain at its early stages by identifying brain connections most affected by early dementia in both hemispheres. We described our findings in section **5.3.3 Analysis of early dementia biomarkers** on page 49 Finally, in section **5.3.5 Limitations and future work** on page 52 we made recommendations for the directions of future research

to further improve upon our proposed framework and contribute to our understanding of early dementia progression in the brain.

Own Publications

[Own1] R. Awan, N. A. Koohbanani, M. Shaban, A. Lisowska, and N. Rajpoot, "Context-aware learning using transferable features for classification of breast cancer histology images," in *Image Analysis and Recognition: 15th International Conference, ICIAR 2018, Póvoa de Varzim, Portugal, June 27–29, 2018, Proceedings 15*. Springer, 2018, pp. 788–795.

[Own2] M. K. Grzeszczyk, A. Lisowska, A. Sitek, and A. Lisowska, "Decoding emotional valence from wearables: Can our data reveal our true feelings?" in *Proceedings of the 25th International Conference on Mobile Human-Computer Interaction*, 2023, pp. 1–6.

[Own3] A. Lisowska and I. Rekik, "Predicting emotional intelligence scores from multi-session functional brain connectomes," in *PRedictive Intelligence in MEdicine: First International Workshop, PRIME 2018, Held in Conjunction with MICCAI 2018, Granada, Spain, September 16, 2018, Proceedings 1*. Springer, 2018, pp. 103–111.

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