Multimodal Data Fusion for Motor Neuron Disease Prognosis Prediction

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I, Florence J Townend, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.

Abstract

Abstract!

Acknowledgements

Acknowledgements!

Contents

List of Figures

List of Tables

Chapter 1

Introduction

Motor neuron disease (MND) is a fatal neurodegenerative condition affecting both upper (UMN) and lower motor neurons (LMN). It encompasses various subtypes, notably amyotrophic lateral sclerosis (ALS), which constitutes a 90% of cases [**?**]. Other subtypes include Progressive Spinal Muscular Atrophy (PMA), Primary Lateral Sclerosis (PLS), and Progressive Bulbar Palsy (PBP), characterised by varying degrees of UMN and LMN involvement. Distinguishing between these subtypes during diagnosis is crucial due to their distinct prognoses and clinical presentations. For instance, PLS tends to have a more favourable prognosis compared to ALS due to less respiratory involvement, offering the possibility of a normal lifespan [2]. Despite advancements, there is currently no cure for ALS, with an average survival time of 3 to 4 years post-diagnosis, although a minority of patients survive beyond 10 years [3, 4, 5]. Incidence rates of ALS vary globally, with European populations and males experiencing higher rates [6, 7].

It is unknown exactly what causes MND, but genetics play a large role. Historically, ALS has been categorised into familial ALS (fALS) and sporadic ALS (sALS), distinguished by whether there is a family history of ALS. However, with 10% of sALS patients exhibiting fALS-associated mutations and a genetic contribution estimated at 61%, there is a blurred boundary between sALS and fALS causes, prompting a reclassification into “genetically confirmed“ and “non-genetically confirmed“ ALS [8, 9, 10]. As of 2022, there have been over 40 genes associated with ALS [4], the most common of which is the C9orf72 hexanucleotide repeat

expansion, which occurs in 5–15% of fALS cases [11]. Apart from genetic risks, there is investigation into environmental risk factors for ALS. A commonly-studied factor is intense physical exercise, including involvement in professional sports and military service [12, 13].

The primary symptom of MND is progressive motor loss in voluntary muscles, sparing involuntary movements like pupillary responses [11]. This progressive motor loss can manifest as reduced limb movement, difficulty swallowing (dysphagia), difficulty speaking (dysarthria), and impaired respiratory function, which is usually the cause of death for MND patients. At symptom onset, this motor loss is usually focused on one body segment, and the weakness spreads in a predictive pattern to the contralateral side in 85% of patients [14]. Ongoing research delves into the incomplete understanding of the neurodegenerative mechanism, particularly focusing on TDP-43 aggregation in the brain, a common feature in nearly all ALS cases [15].

Recently, there's been heightened attention on the cognitive and behavioural aspects of MND, affecting 35 to 50% of ALS patients, with factors like genetics and symptom onset site influencing their occurrence [16, 17]. ALS-FTD, occurring in 15% of cases, is considered a spectrum, with reciprocal links observed, such as 12.5% of behavioural-variant FTD patients progressing to ALS [18]. The most common behavioural symptoms affecting 10% of ALS patients are apathy and loss of sympathy [19]. Other common symptoms are issues with language fluency, social cognition, and executive function [20], although long-term and spatial memory are usually spared [21]. Although these cognitive and behavioural symptoms are not the cause of death of MND patients, increased changes may signal faster disease progression and increased caregiver burden, so it is important to recognise and measure these changes clinically.

There is no definitive diagnostic test for MND, and each patient undergoes a tailored investigation of differential diagnosis. The El Escorial criteria, revised in 2015, categorize patients based on progressive weakness spread, aiding in diagnosis [40]. Diagnostic assessment currently does not include cognitive or behavioural changes, but tools are being developed and more commonly used in order to monitor

these changes, such as ECAS [19]. Due to the length diagnostic process, general unawareness of MND symptoms, and varied speeds of symptom progression, the delay between symptom onset and diagnosis is on average 12 months and roughly halfway through the disease pathway [22].

Disease progression is assessed using the ALSFRS-R (revised amyotrophic lateral sclerosis functional rating scale), a questionnaire evaluating patients' ability to perform disease-related functions such as swallowing or mobility, with scores ranging from 4 (normal function) to 0 (loss of function), yielding a total score ranging from 48 to 0 [23]. While often employed as the primary outcome measure in clinical trials, there is debate over its appropriateness due to its broad domain coverage, prompting suggestions to focus on domain-specific scores like limb movement or bulbar function [24, 25]. Additionally, MND patients may be staged using systems such as the King's Clinical Staging [26] or the ALS Milano-Torino Staging [27], though their widespread clinical adoption remains limited [10, 28].

Common therapies for MND, such as gastrostomy, weight maintenance, and non-invasive ventilation, are standard approaches [29]. In the UK, Riluzole is the primary treatment, potentially offering benefits in advanced stages, with a demonstrated increase in median survival by 3 months [30, 31]. Outside the UK, Edaravone shows promise in slowing disease progression but faces scrutiny regarding trial criteria and safety [33].

Imaging, such as brain magnetic resonance imaging (MRI) and spinal MRI, is currently used in the clinical pathway for MND diagnosis to rule out mimicking diseases. Although not used for prognosis clinically, neuroimaging-derived measures have been shown to be associated with patient survival and progression [63, 65]. Machine learning (ML) is a growing area of research in medical imaging, and its application to neuroimaging been shown to be useful for prognosis in other diseases [**?**]. Moreover, ML has been applied to clinical data for MND prognosis, with some success [**?**, 34].

The work presented in this thesis explores the creation of a machine learning model for MND prognosis prediction using clinical and imaging data from the

diagnostic appointment. The combination of clinical and imaging data is known as multimodal data fusion, and is a growing area of machine learning research, in the medical imaging field and beyond [1, **?**].

1.1 Motivation

Prognosis is the prediction of the course of a disease, and is important for both patients and clinicians. For patients, an accurate prognosis can help them to plan their lives and feel empowered to make decisions about their care [**?**, **?**]. For clinical use, prognosis can be used to stratify patients for clinical trials in order to investigate how different treatments affect different patient groups [**?**]. Additionally, a predicted disease course could be used as an outcome measure for clinical trials [**?**].

Imaging from the diagnostic appointment is a potentially valuable source of data for prognosis prediction. Applying imaging for this purpose would not require any extra data collection, as it is already being taken for differential diagnosis. Morever, a baseline scan is easier for patients to undergo than a scan once their disease has progressed, due to the physical limitations of progressed MND .

Since MND is multifactorial and complex, investigating the value of all available data for prognosis is a logical step. Clinical prognostic factors for MND are well established [36]. Combining these known clinical factors with imaging data could provide a more accurate prognosis than using clinical or imaging factors alone, because these ML approaches are designed to find complex patterns in large datasets that traditional statistical methods may miss.

1.2 Project Aims

The aims of this project are as follows:

Aim 1: To identify factors that are associated with MND prognosis and assess the value of imaging in survival analysis without machine learning.

Aim 2: To explore methods already developed for multimodal data fusion in the literature.

Aim 3: To apply and compare multimodal data fusion methods to MND prognosis prediction with clinical and imaging-derived features.

Aim 4: To investigate the added value of different imaging modalities and preprocessing methods, such as subregion segmentation, texture analysis, and whole brain analysis, in multimodal data fusion for MND prognosis prediction.

Aim 5: To develop the optimal multimodal data fusion model further by adding the capability to include more data modalities, such as fluid biomarkers and natural language processing (NLP) from radiological reports.

Aim 6: To assess how the performance of the proposed prognostic model compares to existing models and clinical prognostic factors, and to assess its suitability to different prognostic tasks, such as stratifying patients for clinical trials or predicting treatment need.

1.3 Upgrade Thesis Outline

Chapter 2 provides a literature review of multimodal prognostic factors in MND, machine learning for MND prognosis, and multimodal methods applied to MND. Chapter 3 presents the results of Aim 1, identifying survival factors in our dataset through Cox proportional hazards models. Chapter 4 describes multimodal data fusion in more detail and outlines the development and design of a Python package, Fusilli, for training, evaluating, and comparing multimodal data fusion methods, and presents the results of Aim 2. Chapter 5 presents the results of Aim 3, applying Fusilli to MND prognosis prediction with clinical and imaging data. Finally, Chapter 6 summarises the findings of this thesis and outlines future work.

Chapter 2

Literature Review

This chapter contains a review of literature on prognosis of MND, looking at both prognostic factors from various data types, and also attempts to predict prognosis using machine learning.

2.1 Prognostic Factors

In MND research, prognosis is often defined as survival time, but it can also be defined as the rate of progression of the disease, future functional ability, the future need for therapies, or a combination of these [34, 35]. In this section, we will review the literature on prognostic factors in MND, and we will group the factors into four categories: clinical, genetic, fluids, and imaging.

2.1.1 Clinical

A large meta-analysis in 2021 collated research studies on non-genetic factors associated with survival risk in ALS [36]. Hazard ratios (HRs), derived from Cox Proportional Hazards (CPH) models, were calculated for each factor which had at least 3 studies reporting on it. The authors conducted sensitivity analyses and heterogeneity analyses to assess the validity of their findings, and found them to be robust.

Some of the factors associated with shorter survival in ALS are well established in the literature, and clinical information about how the disease first presents is a strong indicator of prognosis.

Firstly, an older age of symptom onset is associated with a higher risk of

death [36]. However, it is common in clinical records for the onset date to be the first date of the month or even the first day of the year if the patient cannot remember the exact date, which leads to age of onset being an imperfect measure. Furthermore, a shorter delay between symptom onset and diagnosis is associated with shorter survival [36] because a shorter delay suggests that the disease is fast-progressing and more obvious to clinicians to diagnose. A delay of more than one year indicates longer survival (HR=0.39) [36] and another study showed a delay of less than one year indicates shorter survival (HR=3.43) [37].

Both the site of symptom onset and the speed at which motor symptoms spreads to other sites are associated with survival. Compared to the most common onset site, spinal, Su and colleagues found that bulbar onset (HR=1.35) and respiratory onset (HR=2.2) are associated with shorter survival [36]. A short interval between the first motor onset and the next site involvement is also associated with shorter survival [38], and the speed of motor symptom progression is a prognostic factor independent of the sites themselves.

Extra-motor symptoms are also associated with shorter survival. Executive dysfunction, the appearance of frontotemporal dementia (FTD), and non-specific dementia are all associated with shorter survival and faster disease progression [36, 39].

Both a smaller ALSFRS-R at diagnosis and a faster rate of ALSFRS-R decline are associated with short survival [36]. he rate of decline in ALSFRS-R from onset to diagnosis is also called the progression rate to baseline, or PRB, and is calculated as

$$PRB = \frac{48 - \text{ALSFRS-R}(t_{diag})}{t_{diag} - t_{onset}}, \tag{2.1}$$

where t_{diag} and t_{onset} are the dates of MND diagnosis and symptom onset respectively, and 48 is the maximum score of ALSFRS-R.

Finally, taking Riluzole is associated with longer survival (HR=0.80), and lower forced vital capacity (FVC) is associated with shorter survival [36].

Due to the heterogeneity of MND, there are factors that have mixed associations in the literature. The El Escorial criteria, used to assist ALS diagnosis, assigns

patients into categories associated with the confidence of the diagnosis, from “definite“ to “possible“ [40]. “Definite“ ALS patients have been found to progress faster than “probable“ or “possible“ patients in the meta-analysis and a large multi-centre study [36, 41]. However, in a large cohort of 1,809 Chinese patients, there was no significant relationship between El Escorial and survival [37].

MND is frequently accompanied by rapid weight loss due to feeding and swallowing difficulties, appetite loss, and muscle mass atrophy. A higher body-mass index (BMI) at diagnosis is associated with longer survival in the meta-analysis (HR=0.97) [36], also supported by smaller meta-analysis [42] and a large population study [37]. On the other hand, some studies found that baseline BMI was not important, but rather the rate of BMI decline is a better prognostic factor, both years before disease onset [43] and after diagnosis [44]. More precise measures of body composition, such as MRI of the knees and diaphragm, have found that higher subcutaneous fat is associated with higher ALSFRS-R and lower rate of ALSFRS-R decrease [45].

Statins, a drug that inhibits cholesterol synthesis, has been studied as a prognostic factor in MND. Su and colleagues found no significant effect on survival in their meta-analysis, from three papers reporting non-significant HRs [36]. However, Weisskopf and colleagues found that taking low-potency statins for short durations before diagnosis is protective for survival, but this effect is lost when the duration of statin use is over 3 or the potency of the statin is higher [46]. They suggest that statins might protect ALS survival if used for shorter durations and at lower doses, indicating less severe cardiovascular conditions that could harm survival.

2.1.2 Genetic

Genetic testing after diagnosis is becoming more common because the genetic contribution to MND is better understood and therapeutics are being developed to target specific genetic mutations [47]. A network meta-analysis on genetic factors associated with survival in ALS found that the C9orf72 repeat expansion is associated with shorter survival(HR=1.6) [48], backed up by other large cohort study [49]. Also associated with shorter survival is ATXN2, a CAG repeat expansion usually

associated with spinal onset ALS (HR=3.6), and a mutated FUS (fused in sarcoma) (HR=1.8) [48].

2.1.3 Fluids

Fluid biomarkers are measurements of proteins, metabolites, or other molecules in the blood/serum, cerebrospinal fluid (CSF), or urine that can be used to diagnose and monitor disease.

From the meta-analysis of non-genetic progostic factors, higher levels of creatine kinase and creatinine in serum indicate longer survival [36]. Whereas, higher levels of neurofilament light chain (NfL) in CSF (HR=6.8), NfL in serum (HR=3.7) and albumin in serum (HR=1.52) are harmful prognostic factors.

NfL is the most studied fluid biomarker in ALS. It is a protein that is released into the CSF and blood during the process of neurodegeneration. Although NfL is best measured in CSF through an invasive and difficult procedure, it can also be measured through a simple blood test, albeit in lower concentrations.

NfL levels rise presymptomatically in ALS [50], and the concentration of NfL plateaus around a year after symptom onset [51, 50, 52].

Higher baseline NfL concentration is associated with shorter survival, concluded from consensus of over 20 studies [53]. Dreger and colleagues also found that higher baseline NfL was significantly associated with higher disease aggressiveness, independent of disease accumulation, as estimated by the D50 model [54].

2.1.4 Neuroimaging

Structural MRI is conducted during diagnosis to rule out mimic diseases, but it is not used for monitoring progression due to difficulties in scanning as the disease progresses. Consequently, the majority of imaging studies in MND are cross-sectional at baseline. This section will discuss the associations between brain imaging measures and prognosis in MND, with the caveat that the vast majority of these studies are only on ALS patients.

ALS imaging studies often suffer from small sample sizes and inadequate patient characterisation, meaning that information on clinical phenotypes and genetic

status is often missing, potentially affecting result significance [55]. Furthermore, many studies correlate brain imaging measures with ALSFRS-R, which is a measure dominated by the effects of lower motor neuron degeneration [55]. These limitations result in a large array of inconsistent findings in the literature. In this section, we are explore brain regions implicated in MND prognosis, grouped by their location in the brain.

Whole-brain Measures

Two small studies($N < 35$) reported that lower total grey matter (GM) volume is associated with faster progression, while lower white matter (WM) volume showed no such association [56, 57]. It was concluded that the GM changes occur after diagnosis, making them a potential biomarker for prognosis, and that the WM changes occur before diagnosis, making them a potential biomarker for early diagnosis [57]. However, a study nearly double the size by Trojsi and colleagues found no differences in overall GM or WM damage between fast and slow progressors, both measured by structural MRI and by diffusion tensor imaging (DTI) metrics, such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) [58]. Conversely, two separate studies found that lower overall FA is associated with faster progression [59, 60].

These findings highlight the inconsistency of results regarding whole-brain structural changes in ALS progression. More studies have focused on specific brain regions and white matter tracts, which we will discuss in the following sections.

Motor Cortex and Corticospinal Tract

MND, characterised by upper and lower motor neuron degeneration, affects the motor cortex and corticospinal tract (CST). The motor band sign is a hypointensity in the shape of a ribbon at the precentral gyrus. Both a higher baseline intensity and a greater change over 18 months in the motor band sign has found to be associated poor prognosis, measured by shorter survival and faster disease progression respectively [61, 62].

Studies consistently show that higher FA in the CST and a slower rate of FA decline is associated with longer survival, slower progression, and greater baseline

function [63, 64, 65, 66, 67]. High FA in tracts like the posterior limb of the internal capsule and right superior longitudinal fascicle is linked to better prognosis, similar to findings in the CST [68, 66]. Furthermore, disease aggressiveness, assessed by the D50 model, correlates with white matter density decreases in tracts connecting frontal, parietal, and occipital lobes, as well as with elevated mean diffusivity (MD) and axial diffusivity (AD) in the fronto-parietal tract [69].

Cortical Thickness

Cortical thickness (CT), measured as the distance between the pial surface and the grey-white matter boundary, has shown mixed associations with MND prognosis. CT loss in the temporal and frontal lobes has been correlated with faster progression in small cohorts ($N < 50$) [70, 71]. However, in a larger cohort of 292 patients, the opposite was found: longer survivors had more widespread CT thinning at diagnosis compared to short survivors [72]. It was reported that shorter survivors then went on to have more extensive changes to CT over time, whereas the CT in longer survivors stayed constant. Finally, Dieckmann and colleagues found no association between CT volumes at baseline and D50 disease aggressiveness [73].

The variation in findings on CT and prognosis may relate to MRI timing. Cross-sectional data suggest baseline low CT associates with short survival, yet longitudinal studies are essential to discern whether the rate of CT thinning, rather than initial CT, influences outcomes.

Subcortical Structures

Thalamic atrophy, especially in the right thalamus, correlates with disease aggressiveness and progression rate [73, 74]. Additionally, basal ganglia gray matter atrophy in the left caudate and right putamen is associated with faster progression [59, 75]. Initial smaller basal ganglia and amygdala volumes predict shorter survival, although significance diminishes with age of onset adjustment [76]. Furthermore, texture changes in the basal ganglia and hippocampus, detected via DTI analysis, are notable in short-term survivors [77].

The GM volumes of subcortical structures have been associated with cognitive impairment in other diseases [78]. The association between subcortical structures and

prognosis in MND could be confounded by the presence of cognitive and behavioural impairment, which is not always reported in the studies and is a prognostic factor in MND [36].

Hippocampus

Studies have reported no associations between hippocampal volume [79, 73] or FA [63] and functional decline, measured by ALSFRS-R, progression rate, and D50 disease aggressiveness. Measuring the hippocampus in other ways, Tae and colleagues found that the shape deviations of the right hippocampus is associated with progression rate [80], and Stoppel and colleagues found that increased hippocampal activation in resting-state fMRI is associated with lower ALSFRS-R [81], albeit in small cohorts of 32 and 12 patients respectively.

Frontal Lobe

Some studies in ALS prognosis have focused on the frontal and fronto-temporal lobes due to their known association with FTD, which is a prognostic factor in MND [36]. Fast disease progression has been associated with GM atrophy [59], decreased FA [59, 67], and decrease functional connectivity [58] in the frontotemporal lobe. ALSFRS-R itself has no association with frontal areas FA [63] but has been correlated with reduced functional connectivity in the left sensorimotor cortex [82].

Ventricles

Ventricles are enlarged when the brain atrophies, and larger ventricular volume has been associated with lower baseline ALSFRS-R in a study of 112 patients [76].

Brain Stem

It is expected that the brain stem would be a candidate prognostic marker in MND because it is involved in breathing regulation, and the most common cause of death in MND is respiratory failure. However, Steinbach and colleagues found that brain stem GM density has no affect on D50 disease aggressiveness from D50 [83], and no correlation between brain stem FA and ALSFRS-R was found in a study of 253 patients [63]. Although, in a smaller cohort of 60 ALS patients, baseline medulla oblongata volume significantly predicted short versus long survival [84].

Other measures

Other imaging measures have been linked to MND prognosis. Increased brain age, indicating accelerated brain aging, correlates with faster progression in ALS patients, particularly those with cognitive and behavioral impairment [85]. Notably, significant brain age changes were observed only in ALS patients with cognitive and behavioral impairment, suggesting that brain changes may be more pronounced in these individuals.

Magnetic resonance spectroscopy measures brain metabolite concentrations. Lower N-acetylaspartateto choline ratio in the primary motor cortex is associated with shorter survival, even after accounting for ALSFRS-R and FVC [86].

While findings from neuroimaging highlight the consistent involvement of various brain regions and white matter tracts, including the corticospinal tract and subcortical structures, challenges such as inconsistent results and confounding factors show the importance of analysing imaging data with better patient characterisation through clinical data, especially cognitive and behavioural impairment.

2.1.5 Spinal Cord Imaging

Imaging of the spinal cord can also be conducted during the differential diagnosis to rule out alternative pathologies [87]. The spinal cord is difficult to image and is affected by many movement artefacts due to its small axial size and the proximity of the lungs and heart. Although it is usually qualitatively interpreted clinically, the cross section area (CSA) of the spinal cord has been quantitatively measured in a number of studies, and has been associated with prognosis in MND.

In a study of 43 ALS patients, Branco and colleagues found significant correlations between baseline ALSFRS-R and cervical spine CSA, and also between disease duration and CSA [88]. Moreover, Grolez and colleagues found that a smaller reduction in cervical spine volume over 3 months is associated with longer survival in a study of 41 patients [68]. However, in a study of 218 MND patients, including ALS, PLS, and PMA, the CSA of the cervical spine only correlated with the baseline ALSFRS-R of PLS and PMA patients, although there was no longitudinal spinal atrophy for the PLS patients [89].

2.1.6 Prognostic Models

There are limited clinical tools for prognosis prediction in MND . The most common way for progression to be assessed is through the rate of decline of ALSFRS-R . Extrapolating this progression rate to predict future ALSFRS-R scores is called the "pre-slope model", but it is limited by the assumption that ALSFRS-R decline is linear.

The D50 model assumes ALSFRS-R decline is sigmoidal, and works by fitting a sigmoidal curve to a patient's ALSFRS-R timepoints, yielding an individualised prediction of future ALSFRS-R scores [90, 83]. "Disease aggressiveness" and "disease accumulation" are two measures derived from the D50 model, which are the estimated rate of functional loss and the patient's position on the D50 curve independent of time, respectively.

A non-linear extension of the D50 model was proposed by Ramamoorthy and colleagues, where Gaussian processes are used to non-parametrically cluster patients into non-linear ALSFRS-R trajectories [91]. They found that many of the patients in their cohort had non-linear ALSFRS-R trajectories (convex, concave, sigmoidal).

Westeneng and colleagues developed the ENCALS model, a multivariable Royston-Parmar model, to predict a survival probability function for an individual ALS patient using data from 14 European ALS centres and over 11,000 patient records [41]. The harmful predictors included in the final model are bulbar onset (HR=1.71), age of onset (HR=1.03), El Escorial definite ALS (HR=1.47), higher PRB (HR=6.33), presence of FTD (HR=1.34), and C9orf72 repeat expansion (HR=1.45). The protective predictors are a longer diagnostic delay (HR=0.52) and a higher FVC (HR=0.99).

2.2 Machine Learning for Prognosis

We have seen that prognostic factors have been identified in MND, and that there are a number of prognostic models that have been developed. However, the prognostic models are not widely used in clinical practice, and there is a need for more accurate and generalisable models to be developed. Machine learning (ML) is A potential

solution to this problem is machine learning (ML), which is the use of algorithms to learn from data and make predictions or decisions. In this section, we discuss the literature on ML for MND prognosis using clinical data, imaging data, or a combination of both.

2.2.1 Clinical

As mentioned earlier, prognosis can be defined as the prediction of the future course of a disease. In context of MND, prognosis could be future ALSFRS-R scores, progression rate, survival time, or predicting time until a treatment is needed.

A popular prediction task in ML prognosis is predicting future progression rate, as calculated by the slope between ALSFRS-R scores. In 2011, the DREAM Phil Bowen Prize4Life ALS Prediction Challenge tasked entrants to use 3 months of clinical trials data to predict the progression rate over the following 9 months [92]. This challenge used the PRO-ACT database, which is the largest publicly available dataset of clinical trials data in MND with over 8,500 patients from multiple trials [93]. Although widely used in ML studies, the trials' inclusion and exclusion criteria led to younger patients with fewer functional impairments, and so results using PRO-ACT have limited generalisability to the MND population.

The challenge results reported that random forest and tree-based decision models performed the best [92], and a post-challenge study found highest performance with ensembles of classical ML models [94]. Some unexpected findings emerged, such as a high variability in individual ALSFRSr scores being a strong predictor of progression rate [95] and previously unidentified progression biomarkers such as blood pressures and uric acid. A 2022 revisit using deep learning models found similar performance to classical ML, suggesting further data or tasks may be needed to demonstrate deep learning's benefits [96].

While the Prize4Life challenge was a great catalyst for ML research in MND, predicting linear decline over 9 months is a flawed task. Condensing 9 months of progression into a single slope oversimplifies the disease course, as evidenced by Ramamoorthy and colleagues finding how non-linear ALSFRS-R trajectories are very common [91]. Furthermore, random forests outperform the pre-slope model

in predicting future ALSFRS-R scores, showing that models capable of non-linear calculations are needed for predicting functional decline.

Predicting fast versus slow progression in MND is a common task where patients are labelled based on progression rates [97, 98]. This task often outperforms predicting actual progression rates due to its less granular nature. Training separate models on patient subgroups has also shown to improve performance, either by stratifying on progression rate [99] or on deterioration pattern [100]. The success of these stratification approaches suggests that the heterogeneity of MND may be too great for a single model to predict progression rate accurately.

A more data-driven way of grouping patients is to use clustering, which is a type of unsupervised learning where the model groups patients into clusters based on their features. Grollemund and colleagues used UMAP (uniform manifold approximation and projection) to reduce the dimensionality of patient data, and then coarsely divided the lower-dimensional space into tiers of 1-year survival risk [101]. They found that this approach outperformed random forest and logistic regression in predicting 1-year survival, even though the latent space had no knowledge of the survival times of the patients in the training data.

Another goal in MND prognosis is to predict time to treatment, such as time to NIV or time to PEG (percutaneous endoscopic gastrostromy). The IDPP Clef challenge is a recent challenge in 2022 that focused on predicting risks of clinical events and timings in MND [102]. The 4 resulting papers all found that it was comparatively simple to predict the risk of clinical events, but not the timings [103, 104, 105, 106]. Other attempts at predicting time to treatment have focused on only predicting time to NIV [107, 108]. However, predicting the timing of medical interventions is a difficult task due to varying clinic strategies and interpretations of clinical guidelines. Predicting the assessment outcomes that lead to the decision to start treatment may be a more useful task.

Integrating logical rules and explainability methods enhances the clinical relevance of models in MND prognosis. Tavazzi and colleagues used a dynamic bayesian network to simulate disease course according to the MiToS staging system, incorpo-

rating clinical and biological logic into their model [109]. This allows the model to not only learn from the data, but also to be guided by clinical and biological sense, which should mitigate spurious conclusions after training.

Müller and colleagues used a deep learning longitudinal neural network to predict respiratory impairment in MND [110]. To overcome the "black-box" nature of deep learning methods, they employed an explainability method to find the most important features in the model. They found that their model had learned clinically unintuitive relationships, which brought the model's predictions into question. This shows the importance of explainability methods in MND prognosis, and the need for the model's predictions to make sense in the context of the disease.

In predicting MND prognosis with ML and clinical data, there are various approaches to consider. It is crucial to ensure that the model's predictions align with the disease context and to assess their clinical relevance. A survey of 242 Dutch ALS patients revealed a preference for knowing their exact survival time over a survival category (slow, medium, fast) [41]. However, none of the ML studies have attempted to predict exact survival time. This presents a potential future direction for ML in MND prognosis, which could be more meaningful to patients than predicting progression rate.

2.2.2 Imaging

Machine learning has had success within imaging studies of neurodegenerative diseases, such as Alzheimer's disease [111] and Parkinson's disease [112], but less so in MND due to comparatively small sample sizes. Sample sizes are small in MND, and Computer vision ML models require larger cohorts to train the models, due to the complexity of the models and the need for a large number of parameters to be estimated. Few studies have investigated MND progression using imaging independently of clinical data, often addressing the small sample size issue by using image-derived features instead.

Imaging has been used to predict baseline progression rate using white matter connectivity from DTI [113], and to classify patients into neuropathological disease stages using DTI features of ALS-associated tracts [114]. Both of these studies have

limited clinical usefulness, since it is not necessary to predict a baseline progression rate, and the neuropathological disease stage was not associated with the popular clinical staging systems, King's and MiToS .

Querin and colleagues used FA of the spinal cord and spinal cord atrophy to predict survival in a CPH model, and found that MRI parameters were more predictive than clinical features, albeit in a small cohort of 49 patients [115].

In summary, imaging studies in MND have focused on diagnosis and disease understanding rather than prognosis prediction. Despite the many prognostic factors identified in neuroimaging studies, the limited sample sizes in MND imaging research limits the utility of imaging data alone.

2.2.3 Multimodal

Combining imaging and clinical data could increase the amount of information available to a model and address the suboptimal use of imaging data in MND prognosis. Multimodal data fusion is a technique that combines data from various modalities into a single model in order to accomplish this integration. Due to its multifactorial nature and complexity, MND is a good candidate for multimodal data fusion. Integrating different data sources using ML could help to fully capture the complexity of the disease, and to understand the underlying multifactorial mechanisms of MND progression through the interactions between the different modalities within the model. Furthermore, with limited consensus on imaging prognostic markers in MND, a data-driven strategy guided by clinical data could aid in identifying the most essential imaging findings for prognosis. So far, all of the studies with multimodal data fusion in MND have relied on extracted features from the imaging, rather than the images themselves. However, it is possible to use the images themselves in a multimodal model, and this is a promising future direction for MND prognosis.

Combining clinical and imaging data involves concatenating features from different modalities into a single model, feasible when features share the same dimensionality. However, this introduces the curse of dimensionality, potentially leading to overfitting. Kuan and colleagues found a concatenation multimodal survival model performed similarly to a clinical-only model in predicting survival,

while Schuster and colleagues showed identical test performance between clinical-only and concatenation multimodal models, possibly due to overfitting and the curse of dimensionality. This suggests the concatenation method may have limitations in utilizing imaging data effectively.

To mitigate the limitations of concatenation, other studies have used more advanced methods of multimodal data fusion, such as multimodal dimensionality reduction of the joint data. Behler and colleagues used PCA on concatenated features of cognitive, oculomotor, and DTI to cluster patients into neuropathological disease stages [116]. Kmetzsch and colleagues used a deep learning unsupervised method called a variational autoencoder to lower the dimensions of joint miRNA and structural MRI extracted volumes to predict disease progression in FTD, ALS, and ALS-FTD patients [117]. They found that different modalities were important at different stages of the disease. This insight is an example of how multimodal data fusion can unveil more about the disease than unimodal data alone.

Supervised deep learning is a multimodal data fusion method used in MND prognosis. Van der Burgh and colleagues classified sporadic ALS patients into survival categories using clinical characteristics, structural MRI, and diffusion-weighted imaging features [118], and a later extension added simulated TDP-43 accumulation levels [119]. Their model comprised three unimodal neural networks trained separately and a fourth neural network integrating their outputs, showing significantly improved performance compared to unimodal models. However, an innapropriate statistical test was used to compare the performance distributions. An improved approach could involve training all neural networks together, allowing the intermediate weights and feature maps of the different modalities to interact.

In conclusion, prognosis prediction in MND is a complex task with many different approaches and features that can be used. The literature is afflicted with small sample sizes, inconsistent findings, and unclear clinical relevance, but multimodal data fusion is a promising approach for MND prognosis, and has been shown to improve performance in some studies, with the method of data fusion being important. Furthermore, there are many more multimodal data fusion methods that have not

been explored in MND, such as graph neural networks and attention mechanisms, which could be key in accurately predicting MND prognosis.

Chapter 3

Cox Proportional Hazards Model

3.1 Introduction

Many of the clinical and imaging features that were found to be associated with survival in Chapter 2 were found using the Cox proportional hazards (CPH) model. CPH is a survival analysis model that is used to investigate the relationship between the time to an event and the factors that may influence it.

As a first step in my investigation into the predictive power of clinical and imaging features in MND, I used a CPH model to investigate the relationship between the time to death and the clinical and neuroimaging features that were extracted from the ALS Biomarkers Study and Ospedale San Raffaele MND cohorts.

Previously, Querin and colleagues used a multivariable CPH to compare the predictive power of clinical and spinal cord imaging features in ALS in a cohort of 49 ALS patients, and concluded that spinal MRI measures were more predictive than clinical measures [115]. In this chapter, univariable, unimodal multivariable, and multimodal multivariable CPH models were used to investigate the relationship between the time to death and the clinical and imaging features in a larger cohort of 125 MND patients.

3.2 Data

Data from two studies was used for this survival analysis: ALS Biomarkers Study and Opsedale San Raffaele. Both of these datasets contain clinical information on MND patients and structural imaging conducted during their disease course.

The outcome of interest in this analysis is time to death, censored by date of censorship if recorded in the dataset or date of last data update if not. The Ospedale San Raffaele cohort defines their endpoint as death or tracheostomy, but the ALS Biomarkers Study only defines their endpoint as death.

The clinical features in this study are the patient's sex, baseline ALSFRS-R, diagnostic delay, age at diagnosis, site of onset (categorised as bulbar and non-bulbar), signs of FTD, and their MND subtype (categorised as ALS and non-ALS). These features were chosen for their clinical relevance to survival in MND and their availability in both datasets.

Patients were excluded if they did not have a T1- or T2-weighted MRI within 12 months before or after an MND diagnosis. Regional brain volumes were extracted from the MRI using SynthSeg [**?**], a modality-agnostic deep-learning segmentation tool. A modality agnostic tool was chosen to overcome the inconsistency in MRI protocols within the ALS Biomarkers Study and between the ALS Biomarkers Study and Ospedale San Raffaele's MND cohort. The dimensionality of the 33 regions was reduced to 12 by summing right and left regions and choosing regions relevant to MND pathology. The remaining regions were z-score normalised.

The demographics and clinical characteristics of the patients who were included in the analysis are shown in Table 3.1. Out of the 125 patients, 21 were censored and 104 died during the study period. Censored patients were those who were still alive at the end of the study period (or at the time of data download: 5th March 2024) or who were lost to follow-up before the end of the study period.

3.3 Methods

A CPH model is expressed as

$$h(t) = h_0(t)\exp\left(\beta_1 X_1 + \beta_2 X_2 + ... + \beta_n X_n\right), \tag{3.1}$$

where t is the survival time, $h(t)$ is the hazard function, X are the variables investigated, $h_0(t)$ is the baseline hazard if all the variables were 0. The hazard ratios (HRs) are represented as β, with β_1 being the hazard ratio for the variable X_1. A HR larger

Table 3.1: Demographics and clinical characteristics of the patients included in the analysis. ALSFRSr: ALS Functional Rating Scale-Revised.

Variable	
n	125
Sex, n (%)	
Female	55 (44.0)
Male	70 (56.0)
ALSFRSr, mean (SD)	38.9 (6.4)
Survival (months), mean (SD)	34.3 (27.3)
Diagnostic Delay (months), mean (SD)	13.6 (13.2)
Age at Diagnosis (years), mean (SD)	62.6 (11.4)
Site of Onset, n (%)	
Non-bulbar	91 (72.8)
Bulbar	34 (27.2)
Frontotemporal Dementia, n (%)	
Not present	87 (69.6)
Present	38 (30.4)
MND Type, n (%)	
Not ALS	21 (16.8)
ALS	104 (83.2)
Outcome, n (%)	
Censored	21 (16.8)
Died	104 (83.2)

than 1 indicates the variable is associated with a poorer prognosis, or increased risk of the event, which is death in this CPH application. The assumption of proportional hazards is that each individual in the analysis has the same hazard function, but the hazard functions are scaled by a constant factor, which is not dependent on time. The Python package, lifelines, was used to implement the CPH models and to test the proportional hazards assumption (citation here). Since the aim of this analysis was to see how multimodal data affects survival analysis of MND, four models were run:

1. Univariable model: each feature was tested individually to see if it was associated with survival without adjusting for other features.
2. Clinical-only model: multivariable model with only clinical features.
3. Imaging-only model: multivariable model with only imaging features.
4. Clinical and imaging model: multivariable model with both clinical and imaging features.

The CPH models estimated the hazard ratios and their 95% confidence intervals for each variable, with significance level set at $p < 0.05$.

The quality of models fit to the data was assessed using the concordance index, which is a measure of how well the model predicts the order of the survival times, and the Akaike Information Criterion (AIC), which is a measure of the model's goodness of fit balanced with its complexity.

3.4 Results

3.4.1 Univariable

Table 3.2 shows the HRs, confidence intervals, and significance p values of the features in the univariable CPH, multivariable clinical CPH, multivariable imaging CPH, and multivariable multimodal CPH. The significantly harmful univariable factors are an older age of diagnosis (HR=1.48), co-presence of FTD (HR=1.58), having ALS MND (HR=2.40), and larger volumes in CSF (HR=1.40) and lateral ventricles (HR=1.58). Significantly protective factors include higher baseline ALSFRS-R (HR=0.70), a longer diagnostic delay (0.77), and larger volumes in the brain stem (HR=0.66), hippocampus (HR=0.59), amygdala (HR=0.59), thalamus (HR=0.78), caudate (HR=0.77), putamen (HR=0.72), pallidum (HR=0.75) and cerebellum cortex (HR=0.71). The only features included that did not significantly affect survival were sex, bulbar site of onset, cerebral white matter volume, cerebellum white matter volume, and cerebral cortex volume.

3.4.2 Multivariable

3.4.2.1 Clinical

When the clinical features were input into a multivariable CPH, baseline ALSFRS-R was a significant protective factor (HR=0.62), and ALS MND and older age at diagnosis were significantly harmful (HRs of 1.96 and 1.53). Diagnostic delay and co-presence of FTD were no longer significant in the multivariable CPH.

The proportional hazards assumptions were broken by age at diagnosis ($p = 0.002$) and diagnostic delay ($p = 0.038$). In an effort to correct the broken assump-

Table 3.2: Hazard ratios of survival risk in patients with motor neuron disease for univariable and three multivariable Cox proportional hazards regressions: clinical only, imaging-features only, and clinical and imaging features together (multimodal). Acronyms: FTD - frontotemporal dementia, ALSFRS-R - revised amytrophic lateral sclerosis functional rating scale, CSF - cerebrospinal fluid.

	Univariable		Multivariable					
			Clinical		Imaging		Multimodal	
Variable	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Clinical								
Sex								
Female	1.00, Ref	-	1.00, Ref	-			1.00, Ref	-
Male	0.91 (0.62–1.34)	0.6417	1.13 (0.72 – 1.77)	0.5995			1.11 (0.62 – 1.99)	0.7315
ALSFRS-R	0.70 (0.60–0.82)	<**0.0001**	0.62 (0.51 – 0.76)	<**0.0001**			0.68 (0.53 – 0.88)	**0.0034**
Diagnostic delay, mo	0.77 (0.60–0.99)	**0.0409**	0.79 (0.59 – 1.06)	0.1165			0.86 (0.63 – 1.18)	0.3500
Age at diagnosis, yr	1.48 (1.29–1.84)	**0.0005**	1.53 (1.23 – 1.92)	**0.0002**			1.19 (0.84 – 1.67)	0.3265
Site of onset								
Non-bulbar	1.00, Ref	-	1.00, Ref	-			1.00, Ref	-
Bulbar	1.36 (0.88–2.10)	0.1605	0.90 (0.55 – 1.47)	0.6695			0.94 (0.54 – 1.64)	0.8280
FTD								
No	1.00, Ref	-	1.00, Ref	-			1.00, Ref	-
Yes	1.58 (1.04–2.41)	**0.0337**	1.46 (0.91 – 2.35)	0.1152			1.20 (0.69 – 2.08)	0.5177
MND Subtype								
Non-ALS	1.00, Ref	-	1.00, Ref	-			1.00, Ref	-
ALS	2.40 (1.36–4.23)	**0.0026**	1.96 (1.04 – 3.71)	**0.0384**			2.32 (1.10 – 4.88)	**0.0264**
Volumes								
Brain stem	0.66 (0.53 – 0.83)	**0.0003**			0.64 (0.41 – 1.01)	0.0557	0.64 (0.38 – 1.08)	0.0958
CSF	1.40 (1.16 – 1.70)	**0.0005**			1.10 (0.79 – 1.54)	0.5794	0.93 (0.61 – 1.43)	0.7370
Lateral ventricles	1.58 (1.32 – 1.89)	<**0.0001**			1.52 (1.06 – 2.17)	**0.0214**	1.47 (0.96 – 2.24)	0.0731
Hippocampus	0.59 (0.47 – 0.73)	<**0.0001**			0.96 (0.58 – 1.61)	0.8811	1.18 (0.67 – 2.08)	0.5663
Amygdala	0.59 (0.47 – 0.73)	<**0.0001**			0.65 (0.42 – 1.00)	0.0502	0.68 (0.43 – 1.07)	0.0927
Thalamus	0.78 (0.64 – 0.96)	**0.0173**			1.30 (0.79 – 2.14)	0.2931	1.14 (0.67 – 1.93)	0.6229
Caudate	0.77 (0.64 – 0.93)	**0.0052**			0.62 (0.41 – 0.94)	**0.0245**	0.69 (0.43 – 1.11)	0.1253
Putamen	0.72 (0.60 – 0.87)	**0.0007**			1.30 (0.71 – 2.37)	0.3884	0.88 (0.47 – 1.66)	0.6932
Pallidum	0.75 (0.61 – 0.91)	**0.0041**			0.75 (0.50 – 1.14)	0.1819	0.87 (0.57 – 1.32)	0.5007
Cerebral white matter	0.99 (0.82 – 1.20)	0.9339			2.35 (1.16 – 4.77)	**0.0181**	2.43 (1.16 – 5.10)	**0.0185**
Cerebellum white matter	0.83 (0.67 – 1.02)	0.0775			0.97 (0.56 – 1.66)	0.9054	1.14 (0.63 – 2.05)	0.6714
Cerebellum cortex	0.71 (0.57 – 0.88)	**0.0016**			0.79 (0.52 – 1.21)	0.2888	0.82 (0.51 – 1.32)	0.4135
Cerebral cortex	0.99 (0.82 – 1.21)	0.9462			0.90 (0.45 – 1.83)	0.7769	0.87 (0.41 – 1.84)	0.7118

Table 3.3: Univariable-screened hazard ratios of survival risk in patients with motor neuron disease for three multivariable Cox proportional hazards regressions: clinical only, imaging-features only, and clinical and imaging features together (multimodal). The features included are significant in univariable Cox regressions. Acronyms: FTD - frontotemporal dementia, ALSFRS-R - revised amytrophic lateral sclerosis functional rating scale, CSF - cerebrospinal fluid.

	Univariable (Significant Only)		Multivariable with Univariable Screening					
			Clinical		Imaging		Multimodal	
Variable	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Clinical								
ALSFRS-R	0.70 (0.60–0.82)	<**0.0001**	0.64 (0.53 – 0.77)	<**0.0001**			0.69 (0.55 – 0.88)	**0.0026**
Diagnostic delay, mo	0.77 (0.60–0.99)	**0.0409**	0.81 (0.61 – 1.07)	0.1385			0.83 (0.61 – 1.13)	0.2346
Age at diagnosis, yr	1.48 (1.29–1.84)	**0.0005**	1.52 (1.21 – 1.9)	**0.0003**			1.03 (0.74 – 1.42)	0.8646
FTD								
No	1.00, Ref	-	1.00, Ref	-			1.00, Ref	-
Yes	1.58 (1.04–2.41)	**0.0337**	1.42 (0.89 – 2.26)	0.1429			1.17 (0.69 – 2.01)	0.5561
MND Subtype								
Non-ALS	1.00, Ref	-	1.00, Ref	-			1.00, Ref	-
ALS	2.40 (1.36–4.23)	**0.0026**	2.01 (1.09 – 3.71)	**0.0262**			2.11 (1.03 – 4.32)	**0.0410**
Volumes								
Brain stem	0.66 (0.53 – 0.83)	**0.0003**			0.67 (0.47 – 0.94)	**0.0218**	0.74 (0.51 – 1.06)	0.1041
CSF	1.40 (1.16 – 1.70)	**0.0005**			1.33 (1.02 – 1.73)	**0.0332**	1.24 (0.92 – 1.68)	0.1562
Lateral ventricles	1.58 (1.32 – 1.89)	<**0.0001**			1.63 (1.14 – 2.32)	**0.0072**	1.56 (1.03 – 2.36)	**0.0374**
Hippocampus	0.59 (0.47 – 0.73)	<**0.0001**			1.10 (0.68 – 1.78)	0.7018	1.38 (0.81 – 2.37)	0.2371
Amygdala	0.59 (0.47 – 0.73)	<**0.0001**			0.65 (0.42 – 0.99)	**0.0473**	0.62 (0.39 – 0.97)	**0.0381**
Thalamus	0.78 (0.64 – 0.96)	**0.0173**			1.74 (1.11 – 2.71)	**0.0149**	1.38 (0.86 – 2.23)	0.1844
Caudate	0.77 (0.64 – 0.93)	**0.0052**			0.64 (0.43 – 0.97)	**0.0339**	0.73 (0.46 – 1.14)	0.1609
Putamen	0.72 (0.60 – 0.87)	**0.0007**			1.55 (0.87 – 2.73)	0.1338	1.19 (0.67 – 2.11)	0.5556
Pallidum	0.75 (0.61 – 0.91)	**0.0041**			0.77 (0.52 – 1.13)	0.1779	0.84 (0.58 – 1.22)	0.363
Cerebellum cortex	0.71 (0.57 – 0.88)	**0.0016**			0.81 (0.58 – 1.11)	0.1900	0.86 (0.60 – 1.23)	0.4093

Table 3.4: Metrics assessing the Cox proportional hazards models' fits: c-index (concordance index) and AIC (Akaike Information Criterion).

			Fit metrics	
Model	**Factors Included**	**Number of Factors**	c-index	AIC
Clinical	All variables	7	0.73	799.66
	Univariable-screened	5	0.73	796.40
Imaging	All variables	13	0.75	794.90
	Univariable-screened	10	0.74	799.60
Multimodal	All variables	20	**0.78**	**787.53**
	Univariable-screened	15	0.77	789.11

tions, another multivariable CPH was fit with only the univariably-significant clinical factors. Table 3.3 shows the results from the univariable-screened CPH models. This fixed the broken proportional hazards assumptions and the same factors remained significant: high baseline ALSFRS-R (HR=0.64), age at diagnosis (HR=1.52), and ALS MND (HR=2.01).

3.4.2.2 Imaging

The multivariable imaging CPH resulted in three significant survival factors: lateral ventricles (harmful, HR=1.52), cerebral white matter (harmful, HR=2.35), and caudate (protective, HR=0.62). However, the cerebral white matter and CSF variables broke the CPH assumptions ($p = 0.0325$ and 0.005 respectively).

When only the univariably-significant imaging factors are input into a multivariable CPH, more factors were significantly associated with survival, shown in Table 3.3. Higher volumes of the brain stem (HR=0.67), amygdala (HR=0.65), and caudate (HR=0.64) were protective, and higher volumes of the CSF (HR=1.33), lateral ventricles (HR=1.63), and thalamus (HR=1.74) were harmful.

3.4.2.3 Multimodal

Only three factors were significant in the multimodal multivariable CPH: baseline ALSFRS-R (HR=0.68), ALS MND (HR=2.32), and cerebral white matter volume (HR=2.43). The proportional hazards assumption was broken by sex ($p = 0.0069$), bulbar site of onset ($p = 0.0298$), and cerebral white matter ($p = 0.0497$).

Screening input variables by their univariable significance resulted in a CPH

that had no broken assumptions and four significant survival factors: two clinical and two imaging. Higher baseline ALSFRS-R (HR=0.69) and larger amygdala volume (HR=0.62) were significantly protective, and ALS MND (HR=2.11) and larger lateral ventricle volume (HR=1.56) were significantly harmful.

Table 3.4 shows the metrics of model fit for the multivariable CPH models. The multimodal multivariable models resulted in the best fit metrics, both when considering all the models and also when considering only the univariable-screened models and the "all variable" models.

3.5 Discussion

The univariably-significant clinical factors in this analysis were consistent with the existing literature. However, having a bulbar site of onset was not significantly associated with survival, which was surprising, as bulbar onset is often associated with a poorer prognosis in MND and was found to be significant in a meta-analysis of survival factors [36]. 27.2% of the patients in this analysis had a bulbar site of onset, which is consistent with the general MND population [10], so it is unlikely that the lack of significance was due to a small sample size. Our analysis categorised patients as having a bulbar or non-bulbar site of onset, but a respiratory site of onset is associated with a poorer prognosis than bulbar onset [36], so it is possible that the lack of significance was due to the categorisation of the site of onset. Future work could investigate the relationship between the site of onset and survival in MND by using a more granular categorisation of the site of onset, such as bulbar, respiratory, and limb onset.

However, in general, a univariable model is not the ideal model for survival analysis of a multi-factorial disease like MND, as it does not account for the effects of other variables on the outcome.

The multivariable models all resulted in broken proportional hazards assumptions, which were fixed by screening the input variables by their univariable significance. This approach is not without controversy, as it is possible that features that are not significant univariably are significant in the multivariable model. However,

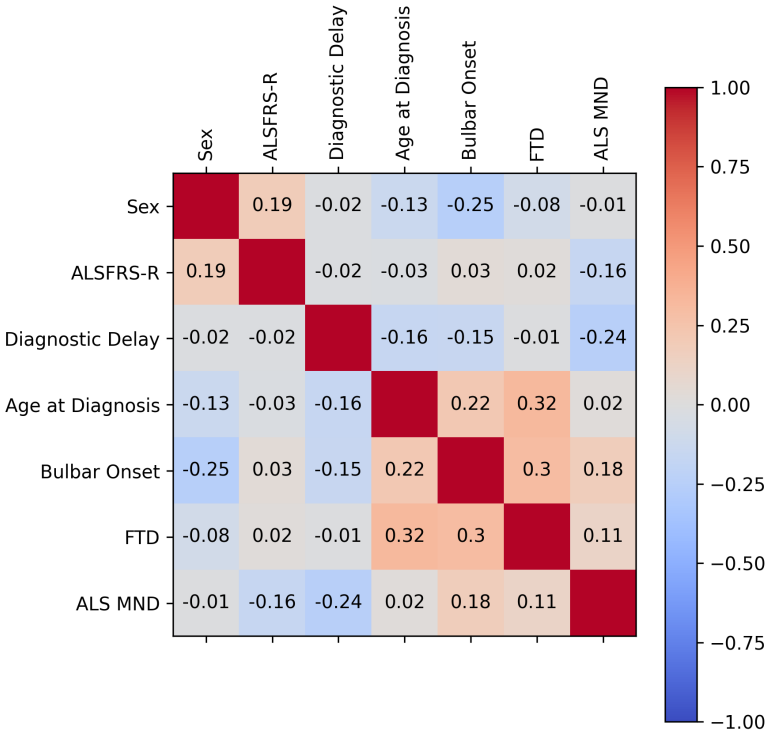

Figure 3.1: Correlation between the clinical features input into the Cox proportional hazards survival model, as calculated by Pearson's correlation coefficient.

we did not find this to be the case in our analysis, since the screened imaging and multimodal models resulted in more significant features than the unscreened models.

Diagnostic delay and FTD lost significance in the multivariable clinical model (both screened and unscreened) when age at diagnosis was included. This lost significnace could be explained by the correlations in the clinical features, shown in Figure 3.1. In multivariable models, the features that are correlated with other features are less likely to be significant, because the effect of the correlated features is already accounted for by the significant features. Figure 3.1 shows that age at diagnosis is the most positively correlated with FTD, which could explain why FTD lost significance in the clinical model when age at diagnosis was included, and age at diagnosis remained significant. Moreover, diagnostic delay is the most negatively correlated with ALS MND, which resulted in diagnostic delay losing significance, even though it was significant univariably.

Imaging model:

- Significant features include cerebral white matter which was not significant in the unvariable model
- Not clinically intuitive - there are papers that suggest that higher white matter volume is better for prognosis
- With the univariable model, more features were significant, and all were clinically intuitive apart from thalamus
- You would expect higher volumes of brain matter would be protective, and higher volumes of CSF and lateral ventricles would be harmful from literature
- Protective in univariable, hazard in multivariable - why? could be to do with the high collinearity still in the model
- It could also be that the model is picking up on brain structure not directly influencing survival, but markers of clinical features that are influencing survival, such as older age at diagnosis, which is associated with brain atrophy, and FTD, which is associated with limbic atrophy.
- Interesting that limbic structures were being picked up as significant: thalamus, amygdala, and caudate. This could be because they are involved with cognitive and behavioural changes, which is a significant factor in MND survival, and was shown to be significant univariably with co-presence of FTD.

Clinical and imaging model:

- Combining the clinical and imaging measures into one model should mitigate the effect of the model picking up on brain structure not directly influencing survival, because we will be including the clinical features that are influencing survival into the model as well
- proportional hazards fixed with uni significant features and resulting features are all clinically intuitive
- Remaining clinical features are consistent with literature, but age at diagnosis was no longer significant.

- A marker of an aging brain is general atrophy, which can be shown by larger lateral ventricles, so it's possible that the model is picking up on the same information from the brain structure as it is from the age at diagnosis, because the lateral ventricles are significant in the multimodal model.

- Inspecting the correlations between the features found that age at diagnosis is correlated with lateral ventricle volume (coefficient of 0.49).

- Moreover, FTD has the most negative correlation with amygdala out of all the brain regions (coefficient of -0.40), which could explain why FTD lost significance in the clinical model when amygdala was included.

- Surprising that the brain stem is not significant in the multimodal model, because it is often implicated in MND survival but it has high correlation with the amygdala (0.6) so this is likely why it lost significance.

- Fit statistics: fit improved with multimodal features - this could be just because we're adding more features, but it could also be because we're adding more information. AIC takes number of features into account, so it's not just that we're adding more features in the multimodal model.

Limitations:

- Small-ish sample size - some of the results may be because of cohort-specific factors, such as including non-ALS MND patients which could be skewing the results. Future work would be to increase the sample size.

- Multi-site without harmonisation - could be that the results are due to site-specific factors, such as MRI protocols and patient populations, that are not accounted for in the analysis

- Scans not generally taken at the same time as diagnosis - MND is a fast moving disease and the brain could have changed significantly between the time of the scan and the time of diagnosis, which could mean that the brain volumes are not representative of the patient's brain at the time of diagnosis. However,

this was a trade off between sample size and data quality. When we increase the sample sizes, we can look at scans taken closer to diagnosis to see if the results are consistent.

- Univariable screening - a controversial approach. It is possible that features that are not significant univariably are significant in the multivariable model. However, we did not find this to be the case in our analysis, and the proportional hazards assumptions were fixed by screening the features, which could mean that the univariable screening was a valid approach in this case.

- Collinearity of the brain volumes was high, which could mean that individual volumes are picked out as significant over others just because they are correlated, even if both are influencing survival. A way around this could be to do dimensionality reduction on the brain volumes, such as PCA, to get a more independent set of features that describe more broader areas of the brain, like in [76].

- Summing left and right regions - could be that the left and right regions are not the same, and summing them could be losing information. However, this was done to reduce the dimensionality of the brain volumes, and the regions were chosen because they are implicated in MND pathology.

Take home message:

- Using imaging-derived feature with clinical features increases concordance, more information into the model is better, makes the clinical measure significant as well when it wasn't before

- Would this result also be sustained when using more sophisticated machine learning models? Instinct says yes because they can handle more features and more complex relationships between features - perhaps collinearity of the brain volumes would not be such an issue

3.6 Conclusion

- Link to next chapter: we've shown that using imaging and clinical together is better than using them alone
- Let's see if we can improve on this by using more sophisticated machine learning models

Chapter 4

Fusilli: Developing a Data Fusion Python Library

Linking sentence from Cox chapter: We've seen how multimodal data affects a survival Cox model in MND. What about machine learning for multimodal data?

This chapter discusses multimodal data fusion in more detail and describe the development of Fusilli, a Python package for multimodal data fusion experimentation and analysis.

4.1 Introduction

Multimodal data fusion is the process of combining data from different sources to make predictions or decisions, often through the use of deep learning. The goal of combining different modalities is to improve the performance of a model by leveraging the relevant information from each modality and fusing them in a way that improves the model's performance. There are many research fields where multimodal data fusion is used, such as in agriculture to predict crop yields and detect diseases [120, 121], in disaster management to analyse response scenarios from audio and social media posts [122], and in robotics to help direct the robots with multiple sensors [123]. Moreover, the types of models used in multimodal data fusion can vary a lot, from geometric deep learning to relatively simple neural network architectures [1].

My PhD investigates multimodal data fusion for predicting MND prognosis, an area with minimal deep learning research [96, 110] and only one model specially-created for deep-learning based multimodal data fusion [118]. Despite systematic reviews on the topic attempting qualitative comparison between models [1, 124, 125, 126], a lack of quantitative comparison necessitates experimentation with many models from other fields to identify the most effective for MND prognosis prediction.

However, acquring a diverse range of models for experimentation is made difficult by the use of variable terminology and the common absence of maintained, quality code available in studies.

A way to address these problems is to create a curated collection of models for somebody interested in multimodal data fusion to consult. As far as I am aware, there are three Python packages that house collections of deep learning based data fusion models: "Multi-view-AE" [127], "CCA-Zoo" [128], and "pytorch-widedeep" [129]. However, each of these packages only includes models with specific frameworks (autoencoders, CCA, and Google's "wide and deep" models, respectively), which limits the variety of models available for comparison.

Therefore, I aimed to develop a Python package for training and comparing multimodal data fusion models with any architecture. This Python package is named Fusilli, as a portmanteau of "fuse easily". Fusilli works by taking the user's multimodal data and training it on a variety of models, and then comparing the models' performances.

4.2 Development and Implementation

4.2.1 Software Design Choices

Before developing Fusilli, the following design goals were set to ensure the package would be useful for a wide range of users and tasks, as well as for my own research.

Modularity: Fusilli should be modular, meaning that the various functionalities within the package should be independent of each other. This would allow for easy addition of new models in the future and easy adjustments to the package's functionality. Testing, which is the process of writing code to check that the package

works as expected, would also be easier with a modular design, and so the package would be more reliable.

Beginner-friendly and expert-friendly: Fusilli should be beginner-friendly, with users able to compare the different models without needing expertise in deep learning or Python programming. This would make it different from other similar packages, which require the user to set up their own experiments.

On the other hand, Fusilli should also be expert-friendly, with users who are more capable being able to change the training parameters, modify the models, and access the trained models for further experiments.

Wide applicability: Fusilli should include a wide variety of models, to ensure that the best model for a given task can be found. Moreover, this would ensure that the package is useful for a wide range of users, as different users may have different requirements for model architectures based on their task and data.

Support for two modalities: The models in Fusilli will support data fusion between either two types of tabular data (e.g. clinical data and brain region volumes data) or between an image and tabular data (e.g. MRI images and clinical data). Again, for wide applicability, Fusilli should be able to handle two-dimensional and three-dimensional images, and tabular data of any size.

Support for different prediction tasks: The prediction tasks that Fusilli should support are regression and classification. From the literature, these are the most common tasks for multimodal data fusion, and are the tasks that I am interested in for my own research.

4.2.2 Implementation

Fusilli was implemented in Python, using the PyTorch and PyTorch Lightning libraries for deep learning. This is because PyTorch is a popular library for deep learning, and is known for its flexibility and ease of use.
The user must specify:

- **Data**: The user's data, which must be in the form of a .csv file for tabular data,

and .pt files for images.

- **Task**: The task that the user wants to perform, which can be either regression or classification (binary or multiclass).
- **Models**: The models that the user wants to compare, which can be any of the models included in Fusilli.
- **Output**: The output directory for the trained models and the results of the experiments.

The user can also specify experiment specifics, which are set to default values if not specified. These are:

- Training and validation data splits.
- Maximum number of epochs to train for, including early stopping.
- Any model hyperparameters or architectures that the user wants to modify.
- Batch size.

After the user has specified these, the user calls two functions in Fusilli to train the models:

- `prepare_fusion_data()`: This function prepares the data for training, including splitting it into training and validation sets and running any model-specific data preparation steps.
- `train_and_save_models()`: This function trains the models on the user's data, and outputs the trained models.

Finally, the user can call functions to evaluate a single model or compare the models, which will output the performance of the models on the user's validation data or external test data. The evaluation figures are saved in the output directory, and the user can also access the trained models for further analysis.

4.2.3 Fusion Methods

A literature search was conducted to find models that could be included in Fusilli. The search criteria aimed to return papers that mentioned machine learning, multimodality, and image and tabular data, with variants of these terms used to capture

Table 4.1: Descriptions of data fusion model categories used in Fusilli, first proposed by Cui and colleagues [1].

Category	Description
Operation-based	Models that fuse data based on operations such as concatenation, addition, or multiplication. This can be done at any point in the model, such as at the input, hidden layers, or output.
Attention-based	Models that use attention mechanisms to weight the importance of different modalities.
Graph-based	Models with a graph structure, such as graph convolutional networks.
Subspace-based	Models that project the data into a joint lower-dimensional space, possibly with deep learning methods such as autoencoders.
Tensor-based	Models that use tensor operations to fuse the data to capture inter- and intra-modality correlations.

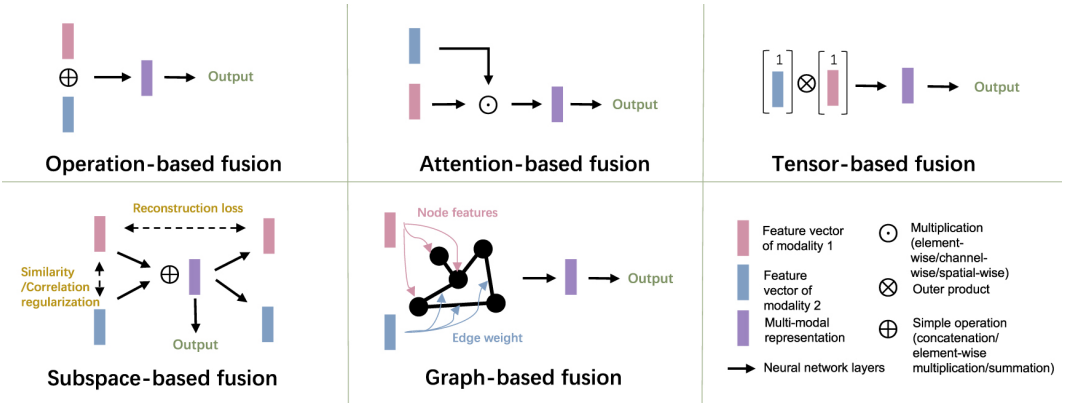

Figure 4.1: Cui and colleagues' diagram of the architecture-based taxonomy of multimodal data fusion models used in Fusilli [1].

a wide range of papers. The resulting papers were checked for relevance and papers were discarded which use the same model as another paper, which happened frequently.

The models were categorised based on the taxonomy defined by Cui and colleagues in their review on data fusion methods for diagnosis and prognosis [1]. Figure 4.1 is a diagram taken from the review, which shows the general architecture differences between the categories, and Table 4.1 includes descriptions of the categories.

Another common categorisation is "early", "intermediate", and "late" fusion,

which refers to the point in the model where the data is fused. However, this categorisation is too simplistic for the variety of models architectures in Fusilli, and so the architecture-based taxonomy was chosen.

More models were found in the literature than were included in Fusilli due to the time constraints of the project, but the models included in Fusilli were chosen based on their popularity, availability of code, and the variety of architectures they represent. Moreover, unimodal benchmarks were included in Fusilli to allow for comparison between the multimodal models and unimodal models.

Table 4.2: A list of the models included in Fusilli v1.2.3, categorised by their fusion method and modalities. References are included where applicable, although the Fusilli implementation is not a direct copy of the referenced model, and may have been modified to fit the package's requirements. **Acronyms**: GNN = Graph Neural Network, MCVAE = Multi-Channel Variational Autoencoder.

Model name (and reference where applicable)	**Fusion**	**Modalities**
Tabular1 uni-modal	Unimodal	Tabular Only
Tabular2 uni-modal	Unimodal	Tabular Only
Image unimodal	Unimodal	Image Only
Activation function map fusion [130]	Operation	Tabular-tabular
Activation function and tabular self-attention [130]	Operation	Tabular-tabular
Concatenating tabular data	Operation	Tabular-tabular
Concatenating tabular feature maps [131]	Operation	Tabular-tabular
Tabular decision	Operation	Tabular-tabular
Channel-wise multiplication net (tabular) [132]	Attention	Tabular-tabular
Tabular Crossmodal multi-head attention [133]	Attention	Tabular-tabular
Attention-weighted GNN [134]	Graph	Tabular-tabular
Edge Correlation GNN	Graph	Tabular-tabular
MCVAE Tabular [135]	Subspace	Tabular-tabular
Concatenating tabular data with image feature maps [136]	Operation	Tabular-image
Concatenating tabular and image feature maps [131]	Operation	Tabular-image
Image decision fusion	Operation	Tabular-image
Channel-wise Image attention [132]	Attention	Tabular-image
Crossmodal multi-head attention [133]	Attention	Tabular-image
Trained Together Latent Image + Tabular Data [137]	Subspace	Tabular-image
Pretrained Latent Image + Tabular Data [137]	Subspace	Tabular-image
Denoising tabular autoencoder with image maps [138]	Subspace	Tabular-image

4.3 Results

Fusilli version 1.0.0 was published on 30th November 2023, and has since been updated to version 1.2.3. Currently, Fusilli is under review for publication in the Journal of Open Source Software (JOSS). The package has been well-received on GitHub, having been favourited by 138 users and specially cloned by 12 users for their own modifications, which is a lot of attention for a package that has only been available for a few months. Moreover, I wrote an article on Medium about Fusilli, which has been read by 243 people, and two articles have been written about Fusilli by other people.

Fusilli is documented using Sphinx, a Python documentation generator. Figure 4.2 shows an overview of the documentation, which includes tutorials for getting started, guidance for more advanced users, example Python scripts which run the models on simple data, a guide for people to contribute their own models, and the source code documentations. The page "Fusion Model Explanations", shown in Figure 4.2B, has a diagram and a text explanation for each model in Fusilli, which is useful for users to understand and compare the models' architectures with a standardised diagram style.

Figures 4.3A, B, and C show the figures output by Fusilli after training, validating, and comparing the models respectively. The format of the figures depends on the prediction task and the type of training used, with the figures shown being for a binary classification task with 5-fold cross validation. If the user chooses to use train-test split training, the comparison figure is a bar chart instead of a violin plot. Additionally, if the user trains a regression model, the performance evaluation will be a scatter plot of the predicted values against the true values.

4.4 Discussion

Overall, Fusilli achieves the goals set out at the beginning of the project. It has had interest from both beginners and experts, and there has been interest from people in different fields, such as thermal imaging. Additionally, a hackathon project was run during the 2023 Centre for Medical Imaging Hackathon, where participants aimed

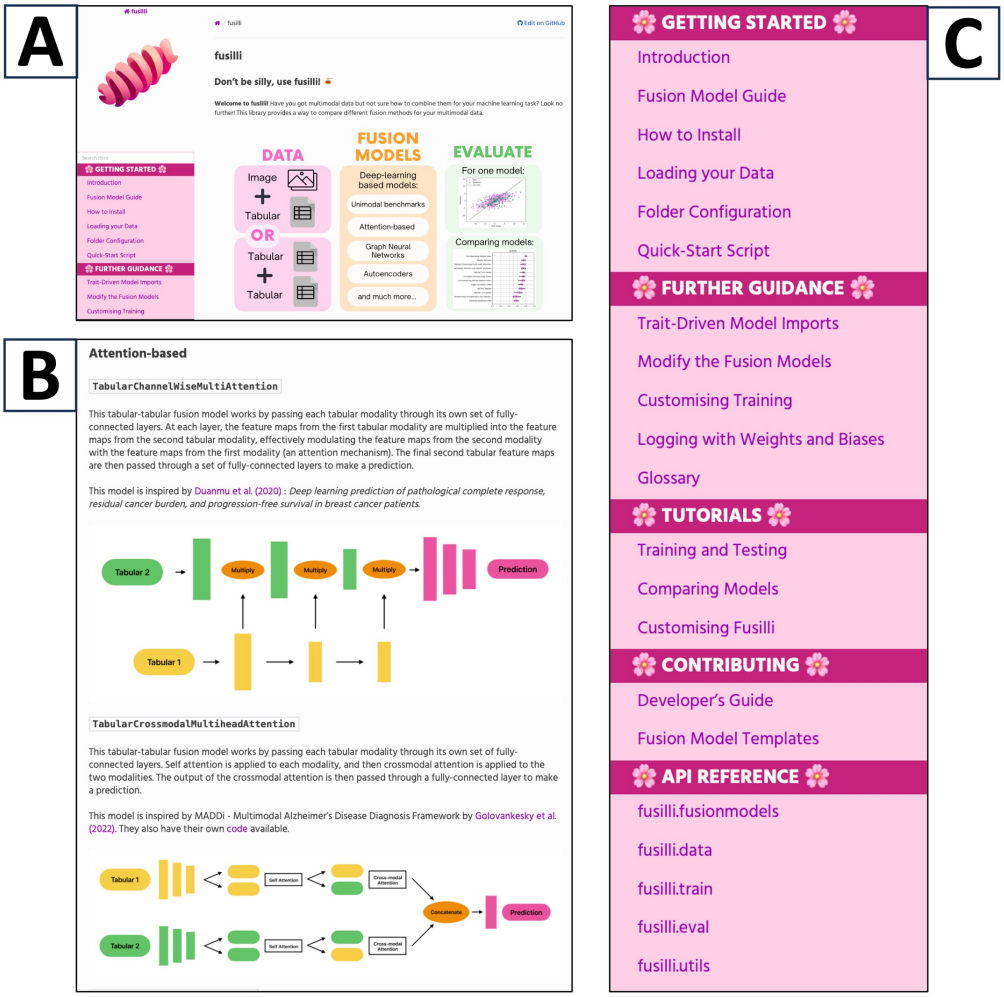

Figure 4.2: Overview of the Fusilli documentation.
A: The home page of the documentation, showing the logo and the diagram explaining Fusilli's purpose.
B: Two examples of the fusion model explanations, complete with diagram and description with reference to source paper.
C: The sidebar of the Fusilli documentation showing all the pages available.

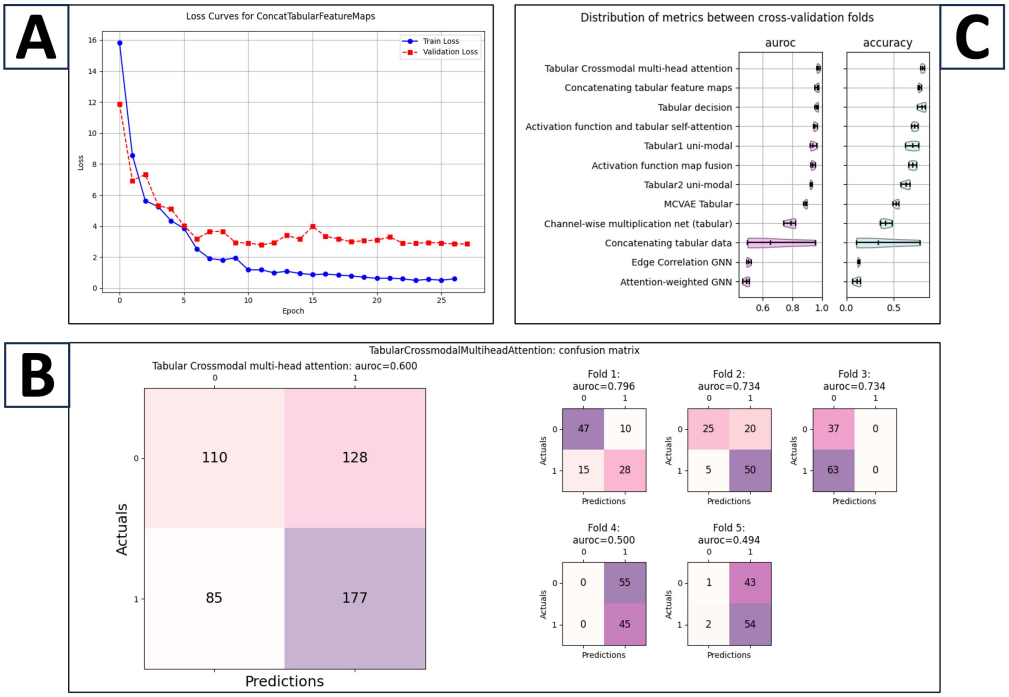

Figure 4.3: Fusion model training, evaluation, and comparison figures output by Fusilli.
A: The training and validation loss curves for an individual model.
B: Performance evaluation of a model which was trained on a binary task with 5-fold cross validation. Both the validation performances of each fold and the overall performance from the aggregated folds are shown.
C: Comparison of the models' performances on the validation data. The violin plot distributions are the distributions of the fold performances when using k-fold cross validation. If train-test split training is used, the comparison figure is a bar chart.

to add new models to Fusilli, which was a success with two new models being added and more in development.

Fusilli has a number of limitations, most of which I hope to address with future updates to the software. Firstly, Fusilli only supports two modalities, which is a limitation for tasks that may benefit from more than two modalities. For example, in the context of MND prognosis prediction, using different types of MRI images (e.g. T1-weighted, T2-weighted, diffusion tensor imaging) could be beneficial, but Fusilli currently only supports one type of image alongside clinical information. Moreover, Fusilli only supports inputting image data the form of PyTorch .pt files, which requires the user to do some pre-processing of their data. This is a limitation

for users who may not be comfortable with Python, and would prefer to input their data in the form of JPEGs or NiFTI files, for example. Fusilli also only supports regression and classification tasks, and does not support other tasks such as time-to-event analysis. Finally, although the models included in Fusilli are popular and cover a wide variety of architectures, there are many more models in the literature that could be included in Fusilli, and I hope to include these.

4.5 Conclusion

In conclusion, Fusilli is a Python package for multimodal data fusion experimentation and analysis, specifically tackling the problem of lack of ways to compare models and lack of standardisation in the field. I specifically made it for my PhD in fusing different data modalities in MND prognosis prediction. The next chapter will discuss the application of Fusilli to MND prognosis prediction, using tabular-tabular fusion of clinical information and brain region volumes.

Chapter 5

Fusilli on MND

5.1 Introduction

Only one deep learning model has been used to predict survival in MND through clinical data and neuroimaging data [118]. This lack of research in multimodal data fusion in MND makes it difficult to conclude whether multimodal data is useful in predicting survival in MND . Additionally, we have shown that many different multimodal data fusion methods have been developed for other research applications. In Chapter 4, we developed a package called Fusilli to compare the performance of multimodal data fusion methods, approximately half of which are designed to combine two tabular modalities.

In this chapter, we will use Fusilli to compare the performance of different tabular-tabular multimodal data fusion methods on predicting survival in MND patients using clinical and imaging extracted features data. The aims of this work are to, firstly, assess the effect of different data fusion model architectures on prognostic performance, and secondly, to assess the value of baseline clinical and neuroimaging data in MND prognosis prediction.

5.2 Data

The data used in this analysis is from two studies: University College London Queen's Square Institute of Neurology's ALS Biomarkers Study [**?**] and Ospedale San Raffaele's MND cohort. Both of these datasets contain clinical data from the diagnostic visit and brain MRI data.

For patients to be included in the analysis, they must have a diagnosis of MND and have an outcome of interest (death or tracheostomy). In the ALS Biomarkers Study, the outcome of interest is death, whereas in the Ospedale San Raffaele's MND cohort, the outcome of interest is death or tracheostomy. Unfortunately, the Ospedale San Raffaele's MND cohort does not specify the date of death, so we have assumed that the date of death is the date of tracheostomy.

Patients in this analysis must have non-missing data for age at diagnosis, sex, date of diagnosis, date of death, date of symptom onset, site of onset, and baseline ALSFRS-R . Additionally, patients must have a T1-weighted or T2-weighted MRI within 12 months before or after their date of diagnosis.

The final dataset contains 110 MND patients. The patients in the cohort were split into two groups based on the median survival time: short survival group (less than 24 months) and long survival group (more than 24 months).

5.2.1 Clinical Data

The clinical variables chosen to be included in the analysis are based on the variables used in the ENCALS model [41] described in Chapter 2. El Escorial criteria and FVC were not included in the analysis as they were not available in the Ospedale San Raffaele's MND cohort. Features with missing data after the inclusion criteria were applied were features of FTD and presence of C9orf72 mutation. Where these features were missing, they were assumed to be negative. Moreover, where the MND type was missing, it was assumed to be ALS, as it is the most common.

Table 5.1 shows the clinical features included in this analysis and statistical differences between the long and short survival groups. The longer survival group had significantly fewer patients with FTD, a longer diagnostic delay, a younger age at diagnosis, and a slower rate of decline in ALSFRS-R . These differences are consistent with the literature on factors associated with survival in MND [36].

Table 5.2 shows the group differences between the two data sites. The cohort from Ospedale San Raffaele had a significantly lower proportion of bulbar onset patients, a higher mean baseline ALSFRS-R score, a lower mean age at diagnosis, and a slower rate of decline in ALSFRS-R .

Table 5.1: Differences in clinical demographics between the long and short survival groups. PRB is progression rate to baseline, calculated as the rate of decline of ALSFRS-R between symptom onset and diagnosis.
*Chi-square test, †Fisher's exact test, ‡ Two-sample t-test.

	Overall	**Short**	**Long**	**P-Value**
n	110	55	55	
Sex (Male), n (%)	52 (47.3)	27 (49.1)	25 (45.5)	0.849*
Bulbar Onset, n (%)	31 (28.2)	20 (36.4)	11 (20.0)	0.090*
FTD, n (%)	32 (29.1)	24 (43.6)	8 (14.5)	**0.002***
C9orf72, n (%)	7 (6.4)	2 (3.6)	5 (9.1)	0.438†
ALSFRS-R, mean (SD)	37.5 (7.2)	36.3 (7.2)	38.7 (7.0)	0.081‡
ALS, n (%)	96 (87.3)	51 (92.7)	45 (81.8)	0.153*
Diagnostic Delay (months), mean (SD)	12.5 (12.0)	10.0 (9.8)	14.9 (13.4)	**0.031**‡
Age at Diagnosis (years), mean (SD)	63.2 (11.8)	69.1 (9.1)	57.3 (11.3)	<**0.001**‡
PRB (points/month), mean (SD)	1.4 (1.7)	2.0 (2.2)	0.9 (0.7)	**0.001**‡
Survival (months), mean (SD)	29.3 (23.2)	12.3 (6.4)	46.4 (21.3)	<**0.001**‡

Table 5.2: Differences in clinical demographics between the two data sites: the ALS Biomarkers Study from University College London and Ospedale San Raffaele. PRB is progression rate to baseline, calculated as the rate of decline of ALSFRS-R between symptom onset and diagnosis.
*Chi-square test, †Fisher's exact test, ‡ Two-sample t-test.

	Overall	ALS Biomarkers Study	Ospedale San Raffaele	P-Value
n	110	46	64	
Sex (Male), n (%)	52 (47.3)	26 (56.5)	26 (40.6)	0.146*
Bulbar Onset, n (%)	31 (28.2)	20 (43.5)	11 (17.2)	**0.005***
FTD, n (%)	32 (29.1)	16 (34.8)	16 (25.0)	0.367*
C9orf72, n (%)	7 (6.4)	3 (6.5)	4 (6.2)	1.000*
ALSFRSr, mean (SD)	37.5 (7.2)	34.1 (8.4)	40.0 (5.0)	<**0.001**†
ALS, n (%)	96 (87.3)	44 (95.7)	52 (81.2)	0.052‡
Diagnostic Delay (months), mean (SD)	12.5 (12.0)	11.9 (10.2)	12.8 (13.2)	0.682*
Age at Diagnosis (years), mean (SD)	63.2 (11.8)	66.2 (12.1)	61.1 (11.1)	**0.028**‡
PRB (points/month), mean (SD)	1.4 (1.7)	1.9 (2.3)	1.0 (1.1)	**0.017**‡
Survival (months), mean (SD)	29.3 (23.2)	24.3 (26.8)	33.0 (19.6)	0.066‡

Statistically significant differences between the sites: **List them here** Why didn't we do any site-specific analysis or correction? - Wanted to see how the model would perform in a real-world setting - Not enough data to do one site

5.2.2 Imaging Data

The same segmentation pipeline used in Chapter 3 was used for this analysis also: using SynthSeg to segment MRI conducted within 12 months before or after diagnosis. SynthSeg returns the volumes of 33 regions of the brain, which, apart from intra-cranial volume, were used as features in this analysis. The region volumes were z-score normalised across the entire cohort.

The left and right volumes were summed to simplify the comparison of regional brain volumes between the long and short survival groups, but the left and right volumes were kept separate for the main analysis. The long survival group had significantly larger volumes in the cerebellum white matter and cortex, thalamus, caudate, putamen, pallidum, brain stem, hippocampus, amygdala, accumbens area, and ventral diencephalon. The short survival group had significantly larger volumes in the cerebrospinal fluid, 3rd ventricle, lateral ventricle, and inferior lateral ventricle.

5.3 Methods

- What are we predicting? Long vs short survival split on the median
- What methods are we using? All the tabular-tabular fusion methods available in fusilli, plus a baseline of just using the clinical data or just using the imaging data
- K-fold cross validation
- To improve the stability of the results, we retrained and reevaluated the models until the mean of the performance of the repetitions converged to *include percentage here*
- Metrics: AUROC and accuracy

5.4 Results

Model comparison figure.

5.4.1 Training together

Table

Figure

5.4.2 Train on one site, test on the other

Train on essex, test on milan

Table

Figure

Train on milan, test on essex

Table

Figure

5.5 Discussion

5.5.1 What does it mean??

Interpreting the results.

5.5.2 Limitations

- Limitations on sample size
- Evaluating on validation set rather than a completely external test set
- Predictive task of classification rather than regression: what if we used a regression task instead? Would that be more useful? It's a harder task so may require more data
- Limitation on using extracted brain volumes rather than raw MRI: what if the regions we've chosen aren't the most important ones? Subcortical regions have shown to have a role in MND, but we haven't included them here. *Look this up - the thalamus stuff*. However, whole image may introduce bias because further progressed patients may have worse quality scans.

- Two sites put together without harmonisation
- Using whole ALSFRS-R rather than individual components - not possible to get with Milan data
- Needs more hyperparameter tuning of the different models to see if they can be improved. Next steps would be to test different network architectures and hyperparameters to see if the results can be improved.

5.6 Conclusion

First look at multimodal data fusion in MND. What does it mean? What are the implications? What are the next steps?

- If imaging + clinical is useful
  - Let's add modalities
  - Let's mix up the imaging preprocessing: DTI? Sub-cortical segmentation?
- If imaging + clinical isn't useful
  - Let's swap out the imaging for other modalities
  - Let's try different machine learning models
  - Let's mix up the imaging preprocessing: DTI? Sub-cortical segmentation?

Chapter 6

Conclusions and Future Work

6.1 Summary and Conclusions

6.1.1 Cox model

- What have I done?
- Why is it useful and novel?
- What did I find out?
- What are the implications?
- What are the limitations?

6.1.2 Fusilli

6.1.3 Fusilli with MND data

6.2 Future Work

6.2.1 Applying Fusilli to MND with clinical, fluids, and MRI data

- Motivation: fluid biomarkers are more accessible than MRI etc.
- Feasibility: ALS Biomarkers Study etc.

6.2.2 Future project 2: Altering image preprocessing

- Motivation: might be better to drill down rather than using whole brain, example papers: ..
- Feasibility: Some methods - toolkits, etc.

6.2.3 Future project 3: Spinal cord MRI data fusion

- Motivation: spinal cord is important in MND, example papers to show this
- Feasibility: Access to spinal cord MRI data

6.3 Timeline

- What have I done so far? Papers and conference submissions
- Outcomes for the rest of my PhD
  - Papers
- Gantt chart

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