Introduction: General MND

General Description

* Standardised global ALS incidence is 1.68 per 100,000, and is higher in populations of predominantly European descent to 1.71-1.89 per 100,000. (Marin et al., 2017)
* Affecting 1.3 men for every woman (Fontana et al., 2021)
* Ancestry and sex play a role in ALS rates (Chiò et al., 2020)

**Diagnostic delay**

* (Mitchell et al., 2010) time from first symptom to diagnosis is around 12 months, roughly halfway through the disease pathway
* Delayed by considering other non-fatal and common illnesses

**Survival time**

* Usually 3-4 years after diagnosis (Swinnen & Robberecht, 2014) (Goutman et al., 2022a)
* 10% of patients live more than 10 years (Pupillo et al., 2014)

Symptoms

**Motor**

Progressive motor deficits in any voluntary muscle(van Es et al., 2017).

* Limb movement
* Swallowing (dysphagia)
* Speaking (dysarthria)
* Respiratory function

**Cognitive + behavioural changes**

* Recognised to occur in 35% to 50% of ALS patients
  + Some patient characteristics are determinants of cognitive impairment - like bulbar onset and C9orf72 status (Yang et al., 2021) (Chiò et al., 2020)
* FTD occurring in 15% of ALS patients, often described as a spectrum (Strong et al., 2017)
* Most common behavioural symptom: apathy and loss of sympathy. Affects 10% of all ALS patients (Abrahams et al., 2014)
* Also fluency, language, social cognitive, executive function (Beeldman et al., 2016)
* Usually long-term memory and spatial memory are not affected (Crockford et al., 2018)
* Important to recognise these symptoms because they are associated with genetic mutations, aggressive disease, treatment recommendation non-compliance, and increased caregiver burden (van Es et al., 2017).

Diagnosis

* No definitive diagnostic test for ALS
* Differential diagnosis instead and investigations tailored to each patient
* **El Escorial diagnostic criteria:** used for patients with history of progressive weakness that has spread (Ludolph et al., 2015)
  + Categorises patients as possible, probable, probable laboratory supported, and definite ALS
* Upper and lower motor neuron involvement may not happen at the same time
  + Differential diagnosis becomes harder - need to look at ALS variants and treatable mimics
* 85% of ALS patients have a focal onset in one body segment that spread predictively e.g. to the contralateral side and to adjacent anatomical segments (Walhout et al., 2018)

Diagnosis does not include cognitive and behavioural changes (Feldman et al., 2022)

Genetic testing will likely become standard practice, especially with therapeutics that are targetting genetic forms of ALS being developed. This will necessicate genetic counselors to have discussions with patients and families. (EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis: et al., 2012)

Types

Types: PLS, PMA, ALS

* Progressive spinal muscular atrophy (PMA)
  + Exclusively LMN involvement
* Primary lateral sclerosis (PLS) (Statland et al., 2015)
  + Exclusively UMN involvement
  + More benign prognosis than ALS because rarely associated with respiratory failure - can live more than 10 years to even a normal lifespan
  + Important to distinguish
* Are these separate diseases or forms of ALS? Debatable (Kim et al., 2009)

Different onset types: (Swinnen & Robberecht, 2014)

* Bulbar and spinal are the two most common presentations
  + Bulbar at more risk of developing FTD (Chiò et al., 2020)
* Respiratory onset and flail arm and leg are less common
* Age, sex, and genetics affect the type of onset as well

Causes

(van Es et al., 2017)

* Genetic compenent: hexanucleotide repeat expansions C9orf72
  + 5-15% patients with ALS, ALS or FTD runs in the family
  + Cause: a single genetic defect
  + More than 40 genes associated with ALS as of 2022 (Goutman et al., 2022b)
  + Most common (and varies by ancestry)
    - C9orf72 (40%) - pleiotropic, linked to FTD, Parkinsons, Huntingtons, Alzheimer's, schizophrenia, bipolar
    - SOD1 (20%)
    - FUS (1-5%)
    - TARBDP (1-5%)
* Sporadic ALS:
  + Environment and genetic risk factors
  + Genetic contribution is still 61% (Al-Chalabi et al., 2010)
  + 10% of patients with sporadic ALS have mutations associated with familial ALS (Hanby et al., 2011)
* Genetics doesn't account for all of ALS incidence so there must be environmental factors (Al-Chalabi & Hardiman, 2013)
* There have been population-based studies for associations between physical exercise and ALS with conflicting results (Lacorte et al., 2016) and military service is often mentioned in ALS risk assessments (McKay et al., 2021)
* Familial vs sporadic is an oversimplication - genetic overlap
  + "genetically confirmed" or "non-genetically confirmed" may be more appropriate (Feldman et al., 2022)

**Pathophysiology**

Mechanisms underlying neurodegeneration

* Not understood!
* Cellular and molecular processes have been implicated
* Nearly all patients with ALS have abnormal aggregation of TDP-43, implying altered TDP-43 function is a disease-causing factor (Blokhuis et al., 2013)

Monitoring disease progression

**ALSFRS-R** (Cedarbaum et al., 1999)

* Scoring patients from 1 to 4 in areas of disability-related function
* These scores are added together with a maximum of 48 and a minimum of 0
* Limitations arise when using the combined score, some suggest using domain specific scores for measuring progression (Rooney et al., 2017)
* Primary outcome measure in clinical trials, but with some controversy with using the combined score (van Eijk et al., 2021)

**Biological measures (?)**

* Hand-held dynamometry can measure decreases in muscle strength
* Also forced vital capacity for respiratory function (Pirola et al., 2019)

**Staging**

* Where is an individual in their disease course? Where should resources be allocated?
* Informing prognosis by categorising patients into defined disease stages (Feldman et al., 2022)
* Examples are King's (Roche et al., 2012) and ALS Milano-Torino (Chiò et al., 2015) but they are not widespread in clinical use (Fang et al., 2017)

Treatments

**Riluzole**

* Anti-glutamate agent
* Only widely-available drug that prolongs survival
* Clinical trials shown to increase median survival by 3 months (Miller et al., 2012) (Hinchcliffe & Smith, 2017)
* Debated whether prolonged survival occurs at all stages of ALS or just in the advanced stages (Andrews et al., 2020)
* Meta-analysis of survival prognostic factors found taking Riluzole to be a protective variable HR=0.8 (Su et al., 2021)

**Edaravarone**

* Not approved in the United Kingdom
* Showed efficacy in slowing disease progression but the trial and repeated trial had restrictive inclusion criteria and questions were raised about its safety and benefits. (Witzel et al., 2022)

Differences in drug availability and decision inconsistencies by regulatory agencies is frustrating for ALS patients, because they feel like they're being denied life-prolonging treatment (van Es et al., 2017).

**Symptomatic therapies**

Treating symptoms can lead to survival benefits and improve quality of life

* Gastrostomy to prevent too much weight loss (caused by loss of muscle, difficulties eating and swallowing, decreased appetite)
* Non-invasive ventilation:
  + Nightly NIV increases survival by 7 months and improves quality of life (Bourke et al., 2006)

**Current trials**

* Focus on now treating patients based on genetic variant(van Es et al., 2017)
* Gene therapy - antisense oligonucleotides (Feldman et al., 2022)
* Monoclonal antibodies
* Anti-inflammatory therapies targeting the immune system

Multifactorial nature of MND

Cognitive and behavioural

(Burrell et al., 2016) **– Link to FTD**

* Overlapping patterns of TDP-43 pathology and shared C9orf72 repeat expansion
* Half of patients with ALS have cognitive and behavioural changes, and a third have language and social deficits consistent with FTD - also in (van Es et al., 2017)

(van Es et al., 2017).

**bv-FTD and ALS**

* 12.5% of patients with behavioural-variant fronto-temporal dementia develop ALS

**Measures of cognitive and behavioural changes**

* ECAS: measure of cognitive and behavioural changes (Abrahams et al., 2014)
* ALS-Brief Cognitive Assessment (ALS-BCA)
* ALS-Cognitive Behavioural Screen (ALS-CBS)
* ALS-FTD-Q

Motor

**Pathology of disease through the brain**

(Brettschneider et al., 2013)

* Begins in pyramidal motor system like the motor cortex, spinal cord, then spreads to neighbouring regions like the prefrontal cortical regions, and then to parietal and temporal lobes and deep grey matter structures.

Clinical prognostic factors

**Large meta-analysis of factors associated with survival in ALS** (Su et al., 2021)

* In 2021!
* Only looking at ALS – not general MNDs (PLS, PMA, PBP)
* Only non-genetic factors considered
* Less than 10% of sporadic ALS have known genetic risks
* Genetic status carries its own risks for survival
* Combining results from papers that reported hazard ratios for factors associated with ALS survival risk
* For a factor to be included, it had to have at least 3 studies with results
* Heterogeneity of studies computed with an I2 metric and Begg’s test
* Sensitivity analysis done on heterogenous results by excluding some research studies
* None of the sensitivity analyses changed significance of findings

Non-genetic

**Demographic**

Age of onset

* Meta-analysis showed higher age of onset has a negative impact on survival HR=1.03 (Su et al., 2021)
* However, this is an unreliable variable because it is difficult for patients to remember exact date of symptom onset. It is common for the onset date to be the first date of the month or even the first day of the year if not properly remembered.

Marital status

* Single patients have a higher risk of early death HR=1.73 (Su et al., 2021)

Smoking

* Current smoker (HR=1.37) and former smoker (HR=1.16) are negative prognostic factors (Su et al., 2021)

**BMI/Weight/Nutrition**

* Baseline BMI
  + (Su et al., 2021)Higher BMI indicates better prognosis HR=0.97. 17 studies were included in the analysis with good heterogeneity score.
  + (Dardiotis et al., 2018) Also agreeing with this smaller (8 study) meta-analysis on only BMI. Conclusion is that a higher BMI at diagnosis is a protective factor (HR=0.96)
  + In a Chinese population, higher baseline BMI also found to be protective (BMI>25 kg/m2 HR=0.36) (Gao et al., 2021)
    - N=1809
  + But (Jawaid et al., 2010) found no significant correlation between progression rate or survival with baseline BMI
    - Wasn’t included in the meta-analyses
  + BMI isn’t a great indicator anyway because it’s not taking body composition into account (Rothman, 2008)
* Greater loss of BMI over 2 years associated with shorter survival and faster progression (Jawaid et al., 2010)
  + N=285, r=0.21 correlation between survival and change in BMI, r=-0.36 correlation between progression rate and change in BMI
* Presymptomatic BMI decrease associated with shorter survival(Goutman et al., 2023)
  + N=381
  + Patients clustered with kNN into decrease, mild decrease, and increasing
  + Decrease had worst prognosis, then increasing, then mild decrease
  + 10 years before diagnosis
* Fat levels (Lindauer et al., 2013)
  + MRI of knees and diaphragm, N=62 ALS
  + Higher subcutaneous fat associated with higher ALSFRS-R (r=0.326), but not visceral fat
  + Progression rate correlated with subcutaneous fat (r=0.311)
  + Increase survival in males with higher subcutaneous fat, but not females

**Cognitive/non-motor**

Executive dysfunction

* Associated with rapid disease progression (Elamin et al., 2011)
* In meta-analysis, a worse survival prognostic indicator HR=2.1

Presence of FTD or non-specific dementia worse prognostic indicators (HR=2.98 and 1.41), according to 2021 meta-analysis (Su et al., 2021)

**Clinical manifestations**

El Escorial scale

* “Definite ALS” progresses faster (Westeneng et al., 2018)
* In (Su et al., 2021), compared to definite, probable ALS had a better prognosis (HR=0.73) and possible ALS was even better (HR=0.6)
* No relationship between El Escorial and survival found in (Gao et al., 2021)
* N=1809

Site of onset

* In (Su et al., 2021), they collected HRs between spinal onset (typical ALS onset zone) and other subtypes
* Worse than spinal: respiratory subtype was the worst prognostic subtype (HR=2.2), then bulbar (HR=1.35)
* Flail arm or leg onset was a better prognostic indicator than spinal (HR=0.61) and predominantly upper or lower motor neuron (pUMN or pLMN) was the best prognostic indicator (HR=0.32)
* (Fujimura-Kiyono et al., 2011) looked at not only the initial site of onset, but also combined onsets and the effects of onset spread on survival
* N=150 sporadic ALS
* Symptom appearances determined from scores of individual ALSFRS-R questions at 3-month follow ups
* “Combined type onset” was significantly worse for survival p=0.01
* A shorter interval between different areas of onset appearing also correlated with shorter survival, even independent of the combination

ALSFRS-R at baseline

* Higher ALSFRS-R indicates better prognosis HR=0.96 (Su et al., 2021)
* (Kimura et al., 2006) found that ALSFRS-R was not a significant factor in survival, only progression rate to baseline is.
* N=82

Progression rate to baseline

* In (Su et al., 2021), where progression rate is categorical or continuous, patients with rapid deterioration had shorter survival (HR=1.48 categorical, 2.37 continuous)
* Similar result with baseline to follow-up progression rate in large Chinese cohort: < 0.75 points per month is protective HR=0.47 (Gao et al., 2021)

FVC

* FVC below 85% is a worse prognostic factor with HR=1.86 (Su et al., 2021)

Diagnostic delay

* Longer delay between symptom onset and diagnosis is a good prognostic factor, when binary longer/shorter than a year (HR=0.39) or continuous (HR=0.97) (Su et al., 2021)
* (Gao et al., 2021) found delay <= 1 year to be harmful HR=3.43 compared to > 1 year. This agrees with Su et al.

**Therapeutics**

Riluzole

* (Su et al., 2021) found HR=0.8 so it’s a protective factor in the papers looking at it

Statins

* Used to inhibit synthesis of cholesterol to reduce risk of cardiovascular-related death
* (Su et al., 2021) found no significant effect on survival for whether ALS survival was harmed or protected by statins use
* 3 papers included, all non-significant HRs on survival
* A paper in 2022 (Weisskopf et al., 2022), that wasn’t included in the meta-analysis, looked also at duration of statins use prior to ALS diagnosis
* N=948 ALS
* Found that taking statins for under 3 years is protective for survival HR=0.77. No effect for over 3 years.
* Taking low-potency statins compared to no statins was associated with longer survival HR=0.82 but not higher-potency statins
* They concluded that statins may have a protective effect on ALS survival but only if the protection outweighs the underlying reason for the statins that may be harmful for ALS survival

Genetic

(Su et al., 2022) They also did a meta-analysis for genetic factors in ALS prognosis!

Looked at variants in **ALS causative/risk genes** with a network meta analysis

* Compared to patients with no known variants:
* C9orf72 HR=1.6 – poor prognosis
* ATXN2 HR=3.6 – poor prognosis
* FUS HR=1.8 – poor prognosis
* Comparing variants against each other1.
* Either having SOD1 or TARDBP had a significantly better prognosis than C9orf72

Looking at genetic modifiers

* UNC13A rs12608932 CC genotype HR=1.18
* ZNF521B rs2275294 C allele HR=1.97

Large study after this meta-analysis: (Chiò et al., 2023)

* N=1,245, not carrying SOD1 TARDBP or FUS
* Because of “heterogeneous clinical course of the different pathogenic variants of these genes”
* In Cox multivariable analysis - independently related to survival:
* C9orf72 HR=1.65
* ATXN2 HR=1.65
* UNC13A HR=1.31
* CAMTA1 HR=1.13
* **Not significant:** ZNF521B
* Copresence of genetic variants that reduce survival significantly
* CAMTA1 and UNC13A
* CAMTA1 and ATXN2
* ATXN2 and UNC13A
* C9orf72 and UNC13A

Tools

**Progression rate to baseline**:

* Equation
* Assumes that ALS functional loss is linear

**D50 model**: (Steinbach et al., 2020) (Poesen et al., 2017)

* Simulated curve of ALSFRSr trajectory based on previous measurements
* Supposed to overcome issues with PR
* Allows for indiviualised predictions of future function
* When normalised, allows for comparison between patients
* “Disease accumulation” and “disease aggressiveness” estimated

**Gaussian processes for non-linear ALSFRS trajectory modelling** (Ramamoorthy et al., 2022)

* ALSFRS slope is linear, D50 is non-linear but parametric
* This paper uses Gaussian processes to non-parametrically cluster patients into non-linear trajectories
* Found that many patients in 5 study populations are non-linear: convex, concave, sigmoidal
* First year ALSFRS slope can wildly over or underestimate future progression
* These progression clusters can correspond to survival outcomes

**ENCALS model** (Westeneng et al., 2018)

* Using N=11,475 ALS patients from 14 European ALS centres
* Multivariable Royston-Parmar model
* Clinical predictors selected to be in the model by doing backward elimination with bootstrapping. Predictors present more than 70% of the time made it to the final model
* Harmful factors
* Bulbar onset (vs non-bulbar) HR=1.71
* Age of onset HR=1.03
* Definite ALS HR=1.47
* Higher progression rate to baseline HR=6.33
* FTD HR=1.34
* C9orf72 HR=1.45
* Protective factors
* Longer diagnostic delay HR=0.52
* Higher FVC HR=0.99
* Concordance c=0.78, and they did leave-one-site-out external validation
* Clustering on the model outputs and the observed outcomes defined 5 groups with distinct median predicted and observed survival times (very short, short, intermediate, long, very long)
* Model is available by request for medical doctors
* More accurately predicted life expectancy of Stephen Hawking (Westeneng et al., 2018)
* Lived for over 50 years after diagnosis
* 10-year survival probability of 94%, IQR between 1981 and 2011 for “survival”, but this can include tracheostomy
* Stephen Hawking had a tracheostomy in 1985
* Model predicting 20% chance of surviving at the time of his death

Imaging prognostic factors

* Imaging is sometimes used in the diagnostic pathway anyway, but only as a differential diagnosis tool
* A review on MRI features that could be used as diagnostic biomarkers (Kocar et al., 2021) looked at 151 studies that compared ALS with healthy controls with some sort of imaging modality
* Less work has been done on how neuroimaging could be used as a prognostic biomarker

**Critical review on imaging in ALS from 2014** (Bede & Hardiman, 2014)

* Looked at 184 research papers and 21 reviews papers
* Found many limitations (which we will see in the following studies), mainly small sample size, suboptimal patient characterisation, technique-driven rather than clinical-driven studies, and insufficient discussion of laterality and symmetry of pathology
* Especially noted was the inconsistency of results from paper to paper – due to the limitations above but also the heterogeneity of ALS

**Neuropathological staging using DTI metrics** (Brettschneider et al., 2013; Kassubek et al., 2014)

* Image-specific staging of disease pathway

**Correlating ALSFRS-R with neuroimaging markers might be unwise** (Bede & Hardiman, 2014)

* ALSFRS-R is heavily influenced by lower motor neuron degeneration which isn’t that captured with brain MRI

Neuroimaging

White matter changes happen relatively early in the disease course, so they are useful for diagnosis, but not so much useful for prognosis or monitoring. Whereas grey matter may be preserved at diagnosis but then degenerate throughout the disease course, making it a better prognostic marker. (Bede & Hardiman, 2018)

* Also shown by (Menke et al., 2014)

### sMRI

Volumetric MRI can help detect atrophic changes in brain structure.

**Increased brain age linked to ALS with c/b impairment**

(Hermann et al., 2022)

* Brain age is how old a brain appears on MRI, and predicted age difference (PAD) is how much older or younger a brain looks compared to healthy people of the same chronological age
* Predicted brain age is based on structural MRI measures and a ML model trained on lots of healthy people’s brains
* PAD has been shown to be a biomarker for lots of diseases, including Alzheimer’s and Epilepsy to name 2, and correlates well with survival and progression in some diseases
* They looked at PAD in ALS patients with and without cognitive or behavioural impairment
* Found that in general, ALS patients did not have a higher brain age
* But ALS patients with cognitive or behavioural impairment did have a higher brain age
* Relationships between increased brain age and faster disease progression and shorter survival time

**Structural measures with D50 model of progression** (Steinbach et al., 2020)

* Correlation between disease aggressiveness and white-matter density decreases
* No link found to GM density
* No difference found between brain stem in patients with aggressive disease – surprising since brain stem is implicated in first phases of TDP-43 accumulation early on in disease pathology

**Subcortical GM and cortical thickness associated with disease accumulation but not aggressiveness with D50 model** (Dieckmann et al., 2022)

* N=100, using the D50 model, investigating associations with cortical thickness and subcortical grey matter volumes
  + Baseline T1W scans
* “Disease aggressiveness” is estimated rate of functional loss e.g. time to half motor function or estimated ALSFRS-R slope at MRI
* “Disease accumulation” is the patient’s position on the D50 sigmoid independent of time
* Lots of associations between disease accumulation and CT/GM volumes
* No associations between disease aggressiveness (time to halved motor function) and CT/GM volumes
* Only the right thalamus volume was significantly correlated with estimated rate of functional loss (estimated slope of ALSFRS)
* Conclusion was that GM is probably independent of disease aggressiveness, and is a better marker of disease accumulation
* **However**, no subjects with cognitive deficits were included, which is a big portion of patients in clinic, and the D50 model is only for estimating time to halved **motor** loss
  + Disease aggressiveness and accumulation is multifactorial

**Looking at extra-motor regions associated with rapid loss of ALSFRS-R** (Senda et al., 2017)

* N=67 sporadic ALS, used ANCOVA
* MRI at diagnosis and then calculated change in ALSFRS-R after 6 months. Split the patients up into 3 groups based on progression change.
* Found that brain regions beyond the motor cortex are implicated in ALS progression
  + Most notably the thalamus and caudate nucleus of the basal ganglia
* Intermediate- and fast-progressing patients had GM atrophy in frontotemporal lobe, which the slow-progressing patients did not
* Rapid progression group had more severe and widespread atrophy generally too
* Relatively small sample size but fits with the picture of the basal ganglia getting involved.

**Baseline GM volume discriminates fast and slow progressors** (El Mendili et al., 2023)

* N=29 ALS, separated into fast and slow progressors based on ALSFRS-R decline
* 3 month and 6 month follow up
* Brain and spine sMRI segmented into volumes:
  + Deep GM structures: accumbens, amygdala, caudate, hippocampus, thalamus, pallidum and putamen
  + Brain stem structures: midbrain, pons and medulla oblongata
  + Spinal cord cross sectional area
* Differences between fast and slow progressors
  + Fast progressors had significantly lower GM and cerebral GM than slow progressors
  + **No significant differences** for cerebellar GM, deep GM, WM, midbrain, pons, medulla oblongata volumes, and spinal cord CSA
* ROC analysis discriminating between fast and slow
  + Total GM volume was the only significant discriminating parameter
  + When separating the GM volumes into cortical, deep, and cerebellar, cortical GM was the only significant discriminating parameter
* Brain and spinal cord atrophy highly correlated with each other
* **Critique:** small sample size and short follow up, but this indicates that fast progressors within 6 months of follow up have noticeable atrophy at baseline in GM. This could be used as a prognostic marker.

**Texture analysis on T1W and relation to short/long survival** (Ishaque et al., 2018)

* N=157, texture analysis on DTI
* Patients divided into long- and short-survival based on median and metric maps from texture analysis compared
* Longer-surviving patietns had texture changes restricted to motor regions and short-surviving patients had more widespread texture changes – including basal ganglia and hippocampus

**Medulla oblongata baseline volume is a predictor of survival** (Milella et al., 2022)

* T1-weighted images *at time of diagnosis*, N=60 ALS patients
* Extracted shape analysis and region volumes specifically of the brain stem
* Survival analysis and ROC analysis on long/short survival clusters
* Medulla oblongata volume was the only significant predictor in univariate and multivariate cox regressions, even over demographic and clinical features
* MO volume had significant accuracy in ROC analysis (AUC 0.76)

**Faster progression associated with more GM atrophy in left caudate and right putamen** (Agosta et al., 2009)

* N=17, tensor based morphometry
* Patients split into fast and slow progressing based on ALSFRS slope
* Faster clinical progression associated with greater GM atrophy in motor and prefrontal areas

**Shorter survival associated with smaller basal ganglia, limbic structures and larger ventricles** (Westeneng et al., 2015)

* N=112 T1W at baseline
* Areas grouped by PCA into ventricular volumes, basal ganglia volumes, and limbic structure volumes
* *Significantly associated with ALSFRS baseline:* larger ventricular volume, adjusted for age and gender
* *With shorter survival*:
  + Smaller basal ganglia (HR=1.44), smaller limbic structures (amygdala and hippocampus) (HR=1.31), larger ventricles (HR=1.31)
  + Lost statistical significance when adjusted for age of onset though

**Cortical thinning in left parahippocampal cortex related to rate of disease progression** (d’Ambrosio et al., 2014)

* N=20
* Cortical thinning in the temporal regions
* Progression measured by change in ALSFRS-R

**Cortical thinning in temporal regions correlated with disease progression** (Verstraete et al., 2012)

* N=45
* Cortical thinning showed significantly negative correlation between thickness and disease progression (rate of ALSFRS)
  + Temporal regions: inferior and middle temporal gyrus
  + Frontal region: right pars triangularis

**“Motor band sign” or hypointensity in motor cortex related to disease progression**

* Signal attenuation in the shape of a ribbon at the posterior border of the precentral gyrus – seen on T2 and also SWI/QSM more recently
* N=7 follow up at 18 months
  + Difference in band intensity after followup significantly correlated with ALSFRS-R progression rate (Boll et al., 2019)
* N=73 cox model
  + Intensity of motor band sign with T2\* or SWI a predictor of survival (HR=2.97) (along with CST hyperintensity HR=4.85) (Rizzo et al., 2020)

### DTI

DTI can reveal changes to the fibre tract in ALS.

**DTI measures with D50 model** (Steinbach et al., 2021)

* DTI instead of structural measures with D50 model: disease aggressiveness calculated by D50
* ALS patients analysed with tract-based-spatial-statistics of FA, MD, RD, and axial diffusivity maps
* Patients with high disease aggressiveness (halved functionality in less than 30 months) had significant MD and AD elevations in fronto–parietal long association tracts
* Corroborates (Steinbach et al., 2020) that WM changes are linked to disease aggressiveness as measured by D50 model

**DTI correlates with ALSFRS-R-measured progression** (Senda et al., 2017)

* Lower FA across the board, and rapid progression group of sporadic ALS (n=67) had more severe and more widespread decreases
* Beyond motor cortex, there were decreases in frontotemporal lobes and the basal ganglia

**Positive association with frontal lobe FA and ALSFRS-R** (Kalra et al., 2020)

* N=66

**Progressive decline in CST FA correlates with progression rate** (Kalra et al., 2020)

* Faster FA decline, faster ALSFRS-R decline
* N=66

**Faster (vs slow) progressing patients had greater reduction in FA of CST and upper frontal lobe** (Kalra et al., 2020)

* N=66

**Positive association between FA in left CST and total ALSFRS-R** (Li et al., 2021)

* N=33
* R=0.468 total ALSFRS-R and FA in left CST

**Higher FA and lower MD at baseline associated with slower progression** (Grolez et al., 2018)

* N=41
* Posterior limb of the internal capsule

**FA of CST at baseline Cox predictor of survival** (Agosta et al., 2010)

* N=24, baseline DT MRI
* Fractional anisotropy of corticospinal tract is a predictor of survival with an HR of 0.97
* Lower average CST FA significantly correlated with higher progression rate (r=0.42)

**Higher baseline progression associated with lower FA and higher RD in left and right corticospinal tracts** (Menke et al., 2014)

* N=60
* Also in right superior longitudinal fascicle and corpus callosum

**Correlation of FA and ALSFRS-R on CST in large study** (Müller et al., 2016)

* N=253
* No correlations found for frontal areas, brainstem, or hippocampal areas
* Comparing groups of patients with different ALSFRS-R decreases showed more widespread white matter involvement with faster disease progression

**Rate of FA decrease and rate of AD/RD ratio decrease correlated with disease progression** (Baldaranov et al., 2017)

* Small sample size of 6, DTI approx. every 3 months
* Whole-brain analysis
* Very high (and significant correlations) of FA decrease and AD/RD decrease with ALSFRS-R decrease

### Multimodal

**Longitudinal brain changes in ALS – links to survival** (Burgh et al., 2020)

* Using structural MRI and DTI measures, looking at cross-sectional and longitudinal imaging features and their associations with disease measures
* *Focusing on results to do with progression and survival*
* ALS changes in the brain happen early on in the disease course
  + Some neuroimaging studies scan people too late, clinical trials should have people more recently diagnosed to prevent brain changes
* Short survivors had more extensive changes in cortical thickness over their longitudinal visits, whereas long survivors had widespread cortical thinning at baseline that stayed relatively constant
* Found widespread loss of white matter integrity, not limited to the CST
* Progressive loss of grey and white matter integrity in short survivors is independent of progression rate
* Short survivors had significant additional cortical thinning in primary motor and frontotemporal regions, long survivors had no significant additional changes

**Hippocampal involvement with ALS disease progression** (Mohammadi et al., 2024)

* A review on looking at hippocampal and parahippocampal attributes with neuropsychological test – since ALS can affect cognitive and behaviour as well
* Focusing on the disease progression findings, there were negative and positive associations found between ALSFRS-R and hippocampal volume from study to study
  + Decreased **bilateral** hippocampal volume associated with disease accumulation as per D50 model, but not disease aggressiveness (Dieckmann et al., 2022)
    - N=100
  + Hippocampal atrophy found in patients with shorter survival (Ishaque et al., 2018)
    - N=157
  + Progression rate negatively correlated with “local shape distances” in **right** hippocampus (Tae et al., 2020)
    - N=32 ALS patients
    - Scalar distances between subcortical nuclei calculated and compared between ALS+HC and ALS+functional rating
  + No correlation between hippocampal volume and ALSFRS-R or progression rate, n=58 (Abdulla et al., 2014)
* Connectivity findings with DTI
  + Disease severity (measured by ALSFRS-R) correlated with reduced left SMC and right parahippocampal gyrus and right cerebellum functional connectivity (Agosta et al., 2011)
    - N=26
* fMRI findings
  + Negative correlation between ALSFRS-R and and increase in hippocampal activation (Stoppel et al., 2014)
    - N=14

**No differences in WM/GM for fast/slow progressors, only differences in connectivity** (Trojsi et al., 2021)

* N=54, fMRI DTI and sMRI at baseline
* Clustered into slow/fast progressors based on rate of ALSFRS-R from diagnosis to 18 months
* From sMRI: No WM or GM damage differences between FPs and SPs
* From DTI: No differences in whole brain DTI metrics, and similar patterns of FA decrease and RD increase in body of corpus callosum and superior part of CST
* From fMRI: FPs had decrease functional connectivity in motor and extra-motor networks
  + (paracentral lobule, precuneus, middle front gyri)
* FPs had increase connectivity in salience network
* No association between connectivity and cognition scores, indicating extra-motor connectivity differences are ALS motor-related

### Other

**MRSI NAA/Cho ratio predictor of survival** (Kalra et al., 2006)

* N=63, magnetic resonance spectroscopy imaging on primary motor cortex
* Cox hazard survival analysis with ratio of NAA (N-acetylaspartate) and Cho (Choline)
* Reduced survival in patients with a lower NAA/Cho (HR=0.24)
* When ALSFRS and FVC added to the analysis (N=32), NAA/Cho remained the only significant predictor (HR=0.14)
* Site of onset did not correlate with survival in the cox model which is surprising, may call into question the other results because bulbar onset is known to be a survival predictor

**Texture analysis metrics from SWI significantly correlated with progression rate** (Johns et al., 2019)

* N=17
* Significant in the left thalamus

Spinal Cord Imaging

(El Mendili et al., 2019)

Difficulties with spinal cord imaging

* Small cross-sectional area in axial plane, long in sagittal and coronal
* Subject to many movement effects from breathing, cardiac movement, and CSF
* Surrounded by structures with different amounts of air with different magnetic susceptibility.

Useful measurements:

* Cross-sectional area to show atrophy.

What is it used for?

* Rule out alternative pathologies
* Qualitatively interpreted.

**No significant correlation between ALSFRS-R and upper spinal cord measurement in ALS** (van der Burgh et al., 2019)

* N=108
* Total ALSFRS- score correlated significantly with baseline upper spinal cord measurement in PLS but not ALS
* But there was a relationship between longitudinal CSA and total ALSFRS-R
* Maybe cervical spinal atrophy is useful for disease progression
* Also had brain MRI measurements, and they did not correlate significantly for ALS patients with spinal cord measurements
  + Capturing different parts of the disease?

**Significant correlation between ALSFRS-R and spinal cord area (CA)** (Branco et al., 2014)

* N=43
* Significant correlation (r=0.309) between baseline ALSFRS-R and spinal cord area
* Significant correlation (r=-0.585) between disease duration and spinal cord area

**Reduction in volume loss of cervical spinal cord associated with longer survival** (Grolez et al., 2018)

* N=41
* Loss within 3 months

Other prognostic factors

Fluids

Meta-analysis in 2021 on prognostic factors in ALS (Su et al., 2021) looked at 5 biochemical factors at baseline:

* Log CK (serum) – higher levels indicate good prognosis HR=0.68
* Creatinine (serum) – higher levels indicate good prognosis HR=0.64
* NFL (CSF) – higher levels indicate worse prognosis HR=6.8
* NFL (serum) – higher levels indicate worse prognosis HR=3.7
* Albumin (serum) – higher levels indicate worse prognosis HR=1.52

pNFH: phosphorylated neurofilament heavy chain in CSF

NFL: neurofilament light chainin plasma/serum/CSF

* Proteins in the neuron that are released during neuroaxonal injury - i.e. when there is neurodegeneration.
* CSF is preferred for clear biomarker concentrations because it is the main reservoir of by-products of neuroaxonal loss, and it is a relatively low-complexity biofluid (Sturmey & Malaspina, 2022).
* Lumbar puncture has to be done to get CSF, which is an invasive procedure and difficult further in the ALS disease course where mobility is limited.
* In (Su et al., 2021) CSF and serum NfL both were significant harmful prognostic factors. CSF has a larger effect because it is closer to the neurodegeneration happening, but it is more invasive for the patient so it’s good the serum is sensitive to the prognosis as well.

**Mention in diagnosis**

* Elevated levels correlate with ALS vs controls (Huang et al., 2020), but are generally elevated in neurodegenerative diseases generally.
* Levels rise in presymptomatic individuals with an ALS gene before showing symptoms (Benatar et al., 2020)

**Prognosis**

Review on neurofilament light chain as biomarkers in ALS: (Irwin et al., 2024)

A few papers have shown that neurofilament concentrations plateau around a year after symptom onset (Benatar et al., 2019, 2020; Thompson et al., 2022)

A general consensus in the literature is reached that higher baseline neurofilament concentration is associated with shorter survival, for the specific list of **22** papers, see the review (Irwin et al., 2024)

However, there is some mixed results whether neurofilament concentration is associated with measures of disease severity such as ALSFRS (Irwin et al., 2024)

In (Thompson et al., 2022) higher baseline plasma NfL is associated with faster rate of disease progression, measured by ALSFRS-R

**D50 disease aggressiveness** (Dreger et al., 2021)

* N=156
* D50 values split into low medium and high
* Highly significant increasing NfL with increasing D50 disease aggressiveness groups
* Independent of gender, onset sites and D50 phase (disease accumulation), but influenced by age, the laboratory, and presence of dementia
* Additional evidence NfL remains stable throughout disease course because there was not association between NfL and disease accumulation independent of time

Machine learning background

For MND

For prognosis: what do we mean by prognosis?

* Anything related to survival time and clinical progression
* Not clustering into groups like (Faraz Faghri et al., 2022) – clinical subtypes but not linked to slow/fast progression

Mention: ML for Diagnosis

Honourable mentions of some MND diagnosis with machine learning papers

**Vision transformer with structural MRI to predict ALS vs HC** (Kushol et al., 2023)

* Using state-of-the-art deep learning to analyse neuroimages

ML for prognosis: clinical data

(Papaiz et al., 2022)

**Review on ML in ALS for prognosis**

Overview of what ML prognosis in MND looks like:

* In 2022, only 10 papers are in the review on ALS ML prognosis
* Various? Survival time, need for support, predicting ALSFRS
  + Can be difficult to predict need for support because it is not only based on patient condition but also clinical decision which varies between clinics

(Tavazzi et al., 2023)

**Another review a year later** on ALS ML for "stratifying ALS patients and predicting disease progression"

* Focusing more on putting patients into data-driven groups, which may correspond to disease severity
* 34 studies this time on progression prediction
* A mixture of regression (predicting time to event as a number) and classification (segregating into groups). Often also seen was survival analyses - mostly Cox Proportional Hazards

**PRO-ACT: common data set** (Atassi et al., 2014)

* Clinical trials data - most widely used for ML with ALS because it's longitudinal and has a large sample size
  + Largest publicly available dataset of ALS clinical trials
* Not very generalisable because of its inclusion and exclusion criteria: patients are younger with fewer functional impairments

**DREAM Prize4Life ALS Prediction Challenge** (Küffner et al., 2015)

* $50,000 award
* In 2015
* Using 0-3 months of trial data to predict months 3-12 disease progression as slope of ALSFRS-R
* 37 entries, classical machine learning techniques

**IDPP CLEF Disease Progression Challenge** (Guazzo et al., 2022)

* Focusing on disease progression as risks of clincial events: percuteanous endoscopic gastrostomy, NIV, death
* Patients records from Italy and Portugal: 2559 patients and 68 variables, 49 of which static and 19 dynamic
* Using AI to do two tasks:
  + Rank subjects based on risk of occurrence of clinical events e.g. will this subject have a gastrostomy before death, will this subject need NIV before death
  + Predict when clinical events will occur
* 4 papers on the progression tasks: (Branco et al., 2022; Mannion et al., 2022; Pancotti et al., 2022; Trescato et al., 2022)
* General results:
  + Similar performances all round: pretty easy for risk prediciton but difficult for time-to-event because of class imbalance.
  + High specificity, low recall for all models
  + Different ways to deal with longitudinal data but all roughly the same results: pattern mining (Branco et al., 2022), weighted averaging (Mannion et al., 2022), slopes (Trescato et al., 2022), min/max/std/highest/lowest (Pancotti et al., 2022)
  + Including dynamic variables in first 6 months of disease improved models when compared with only static (Trescato et al., 2022)
    - (Pancotti et al., 2022)reported average of 0.3-0.4 c-index improvement in task 1 and also improvement in task 2
  + Individual ALSFRS scores better than domain-grouped or total (Mannion et al., 2022)

Classical machine learning

What is classical machine learning? Why can it be useful?

**XGBoost and BLSTM on longitudinal PRO-ACT to classify fast/slow progressors on ALSFRS-R rate of change** (Din Abdul Jabbar et al., 2023)

* PROACT data
* Classifying "fast" or "non-fast" progressors based on their rate of change of ALSFRS-R
  + At least 1.5 points decrease per month
* Using various observation windows and prediction windows
* Models: XGBoost and BLSTM
* Got AUROCs between 57% and 75%: similar performance to clinicians: "non-inferior"
* 3 most important features were days since disease onset (smaller in fast progressors), past ALSFRS-R (smaller in fast progressors), and FVC (smaller in fast progressors)

**Comparing single and ensemble models to predict future ALSFRS slope with PROACT** (Turabieh et al., 2024)

* Compared 17 classical ML models and 5 feature selection models on predicting future ALSFRS slope
* Found ensemble models worked better than single models

**IDPP CLEF predicting time window with two-layer classification** (Branco et al., 2022)

* Predicting which event will occur with random forests and then time to event with a selection of classical machine learning techniques
* Used pattern mining algorithms to deal with longitudinal data
* High performance on predicting which event will occur but low performance on when

**IDPP CLEF hybrid classifier/regressor for time-to-event** (Mannion et al., 2022)

* Same set up as (Branco et al., 2022), but used temporal-weighted averaging to deal with longitudinal data rather than pattern mining
* Separate ALSFRS-R scores performed better than domain-grouped or totally grouped
* Concluded that the survival-classsification/regression approach they did was not appropriate for this analysis
  + Again easy-ish to predict which event, hard to predict when

**IDPP CLEF survival analysis models** (Trescato et al., 2022)

* Using survival analysis models: Cox, SSVM, survival RFs
* Similar results to other entries: good classification, poor time-to-event (high specificity, low recall)
* Saw marked improvements in all tasks by including dynamic features in first 6 months

**IDPP CLEF deep survival models** (Pancotti et al., 2022)

* Deep survival models, naive multiple event survival, time-aware classifier ensemble
* Including dynamic variables improved performance: average increase of 0.3 to 0.4 in concordance index in predicting risks, and also beneficial in time-to-event
* Same as other models: highly specific, low recall due to class imbalance

**Tollgate-based ALS Staging System (TASS)** (Dalgıç et al., 2019)

* Staging system like King’s and MiToS but based on “tollgates” in a disease pathway – critical events like needing a wheelchair or using a feeding tube
* Created an ALSFRSr to TASS mapping (Dalgic et al., 2021) using logistic regression
* Can predict timing of critical events

**Dynamic Bayesian Networks to predict timing of events** (Tavazzi et al., 2022)

* Using baseline patient data and DAGs to simulate the disease course – according to the MiToS staging system
* Applying clinical and biological sense to the model: not letting impossible relationships exist and making some mandatory
* Not limited to only predicting survival, but can also predicting timing of impairments
* Can look at effects of changing some variable on overall disease course
* User-friendly dashboard for clinical use

**Classifying fast/slow progression and high/low death risk with PROACT** (Ong et al., 2017)

* Binary classifications on ALSFRSr progression and survival
* Tried AdaBoost, Naïve Bayes, Decision Tree, Random Forest
* AUCs between 0.75 and 0.85 for all predictions: either using baseline data or using trajectories of longitudinal data (fit to exponential distributions)
* Best variables for the predictions were lab values: bilirubin, bicarbonate, gamma glutamyltransferase, chloride, urine specific gravity
* ALSFRS is strongly associated with survival but not a strong predictor

**Predicting need and time window for NIV with patient snapshots** (Carreiro et al., 2015)

* Creating “snapshots” of patient data by clustering temporal data (clinical data is rarely nicely intervalled)
* Predicting whether a patient will need intervention at 3 time points, short medium and long
* Tried lots of classical machine learning models
* AUC values hovering around 78% for short medium and long term prediction of NIV need

**Predicting need and time window for NIV with conformal predictors and MoE** (Pereira et al., 2019)

* Predicting need for NIV and window (less than 90 days, 90 to 180, 180 to 365)
* Best model is SVM with polynomial kernel
* Incorporating a “reliability score” by using conformal prediction.
* When including low reliability classifications, low sensitivity – improves when only classifying patients with higher reliability (otherwise “unclassified”)
* Using mixture of experts leads to more patients being classified with high probability

**Stratifying patients on ALSFRS-R slope before predicting NIV with ML** (Pires et al., 2018)

* Place patients into 3 groups based on low, medium, high progression rate to baseline
* Predicting need for NIV within 90, 180, and 365 days of appointment
* Train separate models for the separate progression groups: decision tree, KNN, SVM, Naïve Bayes, Random Forest, Logistic Regression
* Feature selection ensemble to see what features are important to the prediction: age at onset, BMI, disease duration, ALSFRS, FVC, VC (selected 75% of the time)
* Models perform better on stratified groups rather than all together
  + When input all data, model performs well for the subgroup with most people in it (neutral progression) and over or under classifies slow/fast progressors
  + Individual models mitigates this

**Clustering based on deterioration then predicting next ALSFRS value** (Halbersberg & Lerner, 2019)

* Clustering deterioration patterns on PROACT patients using temporal data
* Separate classifier for each cluster
* Adds whether a deterioration pattern is present in the patinet as a feature
* Predicting the ALSFRS-R value at the next appointment – is that actually that useful?
* Found that derived deterioration patterns are helpful in ALSFRS-R prediction - but not as much as the measurements from the previous appointment

**Random forests to predict ALSFRS slope with PROACT** (Hothorn & Jung, 2014)

* Came 3rd in Prize4Life challenge
* Found that higher variability in individual ALSFRS question scores implied larger ALSFRS-R slope
* Past disease progression is a strong predictor for future disease progression

**Random forest to predict ALSFRS with PROACT baseline data** (Taylor et al., 2016)

* Predicting progression from baseline data: progression defined as future ALSFRS-R
* Comparing to the pre-slope model, which assumes maximum ALSFRS-R score at time of onset with a linear equation passing through the diagnostic ALSFRS-R
* Random forest outperformed pre-slope model, especially when predicting later time points

**Dimensionality reduction via UMAP to predict 1-year survival probabilities** (Grollemund et al., 2020)

* Incorporating result uncertainty into the prognosis prediction
* UMAP to reduce dimensionality of patient data, then latent space divided into 3 groups on 1-year survival rate
* This is done by taking small bits of latent space and assessing survival rate of the “training set” of that part of the latent space
* New data is projected to latent space and assigned a group
* Compared to RF and logistic regression and assessed with external data – outperforms the ML
* Pros: technically no machine learning is required because UMAP is a dimensionality reduction technique only
* They say that they’re “limiting prognosis error by making a coarse prognosis estimate” - an interesting way to say “being vague means we get stuff less wrong”

Deep learning

**Deep learning on PROACT shows similar results to classical ML** (Pancotti et al., 2022)

* Using deep learning on PROACT since all the entries in 2015 were classical and the science has come along a way
* Same goal as the DREAM challenge
* Comparing three deep learning models, FFNN, CNN, and RNN: two use longitudinal data and one uses baseline + summary
* Found that all deep learning models performed similarly and also performed similarly to the classical machine learning models trained on the same data

**Predicting breathing capability with RNNs** (Müller et al., 2021)

* Longitudinal data (n=1166) with respiratory tests, nerve motor amplitude, ALSFRS
* Predicting number between 0 and 1 to represent respiratory impairment (1 means non-invasive ventilation, 0 means no respiratory issues)
* SHAP values for explanations: resulted in some clinically counterintuitive results, like better swallowing functionality indicates quicker respiratory decline
* Neck strength (measured by cervical extension) is an influential predictor which is clinically backed by other studies
* Confusing explanations can be attributed to patient heterogeneity or maybe high model complexity

ML for prognosis: imaging

Very much a diagnosis-heavy environment

Neuro

**Classifying ALS into neuropathological stages with DTI metrics** (Behler et al., 2022)

* Separating ALS patients into pTDP-43 stages (Brettschneider et al., 2013) using DTI metrics specific to the tracts in question
  + Corticospinal tract
  + Corticorubral and corticopontine tracts
  + Corticostriatal pathway
  + Proximal portion of perforant pathway
* Has been done before with simple thresholding (Kassubek et al., 2014) of FA values compared to healthy controls
* This paper uses bayesian classification with FA values in the specific tracts to classify disease stage, and the algorithm allows for uncertainty measures, whereas the thresholding system does not
* With 325 ALS patients, 88% could be assigned to a DTI stage compared to 77% when using thresholding
* No association between clinical staging (King’s or MiToS) and DTI stage, and disease duration and ALSFRS-R did not differ between stages
  + But there was a trend for lower scores in the higher stages
* This prognostic approach has limited clinical application since the staging does not apply to the patient experience directly, but may have some applicability in clinical trials that focus on TDP-43 pathology

**Predicting baseline progression rate from white matter connectivity** (Li et al., 2021)

* N=73 sporadic ALS
* Weirdly predicting the baseline progression rate using nested cross validation and PCA then SVM
* Baseline progression rate binarized into fast/slow based on 0.68 points per month which was used in other studies (Kimura et al., 2006)
* Found mean balanced accuracy of 85%
* Top contributing connection was left hippocampus to right thalamus

Spinal

**Cox model for spinal cord atrophy**

(Querin et al., 2017)

* Cox model to investigate relationship between spinal cord atrophy and progression
  + Survival analysis to death or censorship
* Used structural MRI for atrophy measures and DTI for fractional anisotropy
* MRI parameters seemed to be more predictive than clinical parameters in their (small n=49) cohort
* Atrophy at multiple points in the spinal cord was associated with faster disease progression

Other

Multimodal imaging

**Random forests combining brain structure and brain function**

(Thome et al., 2022)

* Classifying between healthy controls (HCs) and ALS patients
* Multimodal imaging only - no clinical characteristics apart from regressing out age
* Imaging: structural MRI and resting state functional MRI
  + Extracted volumes from structural MRI
  + Functional connectivity from rsfMRI
  + Non-linear network dynamics from rsfMRI, extracted using RNNs
* Used random forests to make models with all combinations of input data
* Multimodal models outperformed all unimodal models, however the highest accuracy was only 66.8%
* Feature importance scores indicated functional connectivity features were most important for classification
* Most important features had no significant correlation with ALS clinical characteristics such as symptom duration and progression rate

Data fusion in MND

People have done multimodal imaging studies with ALS, and also clinical ML studies - what about combining imaging with other types of data?

**Example of interaction between clinical and imaging data that would provide more information:**

* Handed is associated with site of onset (Turner et al., 2011), and site of onset is a prognostic factor
* And handedness has a link with corticospinal tract/motor cortex asymmetry, which is implicated heavily in ALS (Hervé et al., 2009)

Diagnosis

**Classifying ALS MRI phenotypes with WM, GM, clinical data**

(Rajagopalan et al., 2023)

* Classifying ALS clinical/radiological phenotypes and controls
* They previously looked at WM and GM signatures in these phenotypes
* Random forests and NNs to classify these and neurological controls
* Data from T1W MRI and DTI, and clinical characteristics
* WM measures were more useful than GM measures
  + Fits with theory of WM being degenerated before diagnosis (therefore good for diagnostic classification) and GM degenerating after diagnosis
* Feature importance analysis shows clinical characteristics consistently being most important for classification: progression rate, symptom duration, El Escorial
* WM and clinical measures together led to overall performance improvement from separately

Prognosis

**Clinical features and cortical thicknesses together in non-deep learning models**

(Kuan et al., 2023)

* **N=220**
* Predicting a patient's individual survival distributions (ISD), which is the probability of survival at future time points
* Survival is composite respiratory failure: death, tracheostomy, or NIV for more than 23 hours a day
* They compared 4 ML models and input clinical only, cortical thickness only, or both into the models - just by concatenating
* Their best model had an MAE of survival at 14.2 months, which is better than a non-individualised Kaplan-Meier estimate
* The best model was using clinical only, but the performance was not statistically significantly better
* They used relatively simple survival models and cortical thickness measures
  + Perhaps suggests that either MRI isn’t useful (which we’ve seen from other papers that it is) or that using cortical thickness only is not a good measure to choose
  + Employing deep learning architectures on whole brain MRI rather than extracted features may have more predictive power

**PCA of extracted features to stratify by TDP-43 stage**

(Behler et al., 2022)

* Using clustering to group patients with ALS in an unsupervised way.
* Using multimodal data: DTI, oculomotor, cognitive data.
* Trying to stratify by neuropathological disease stage.
  + What is that? pTDP-43 distributes in a sequential pattern in the CNS in ALS.
  + DTI can show it in vivo.
* The data fusion:
  + Extracted measures from DTI (FA along various ALS-related tracts) and from oculomotor function.
  + PCA on concatenated features to lower the dimensions, then did unsupervised clustering.
* Benefit of data fusion in this work:
  + Can see the interactions between measures within the clusters (or suspected disease stages) and what happens when.
  + Can see what parts of the brain are associated with oculomotor and cognitive behaviour
* Limitations:
  + Extracted features from DTI: could be losing information by doing that
  + Clinical benefit: DTI not usually given in MND clinical care, and clustering into neuropathological

**Disease progression modelling from miRNA and neuroimaging**

(Kmetzsch et al., 2022)

* Looking at C9orf72 carriers and predicting their "disease progression score" (DPS) from their miRNA and extracted volumes from T1W MRI
* Not only ALS focused, only 7 out of the 110 subjects had ALS or FTD-ALS
* Supervised variational autoencoder to create a latent space, where a new patient's coordinate on that latent space is their DPS
* Their main result was comparing their model to our DPMs
* Ablation study looked at the impact of each modality separately for each of the clinical classifications (control vs presymptomatic vs patient) and found that different modalities were the most important at different stages
  + Supporting that the multimodal data is important in predicting disease progression in this case
  + Maybe in predicting actual survival too?

**18-month survival prediction using clinical and MRI features with ridge regression**

(Schuster et al., 2017)

* Predicting classification of 18-month survival from MRI
* n=60 sample size of ALS patients
* MRI features from T1 structural and DTI - chose the features based on comparison with matched controls to find ALS-pathology specific regions
* Using a relatively simple model of binary logistic ridge regression
* Test set (n=12) showed identical performance for clinical-only and clinical with MRI, but the training set performed better with clinical with MRI
* Potentially a marker for overfitting because of the small sample size and higher number of features when combining clinical data with the larger number of MRI features
  + Model can't generalise to unseen data
* Rather than just concatenating the clinical and MRI features together, a more sophiscated fusion approach may lead to better test performance

**Deep learning with clinical, morphology, and connectivity data to predict survival classification**

(van der Burgh et al., 2017)

* n=135 sporadic ALS patients - predicting short/medium/long survival
* Using clinical characteristics, T1W MRI extracted features, and diffusion-weighted images extracted features
* Using deep learning models:
  + 3 unimodal networks trained separately
  + 1 multimodal network using the trained output class probabilities of each unimodal network concatenated as its first layer input
* On a held-out test set, they found the multimodal network had a marked improvement compared to the unimodal networks of 84% compared to the unimodal networks hovering between 60 and 70%
* They take this to mean that combining information from the 3 sources leads to a more informative prediction
* **Thoughts:** 
  + Training the networks separately doesn't allow optimum exchange and interaction between the modalities since the intermediate weights and feature maps from the node layers never interact: perhaps even better performance would be seen by doing that
  + Inappropriate method to calculate statistical significance of differences in results because they used number of repeats instead of sample size

**Extending van der Burgh model with simulated TDP-43 aggregation levels**

(Meier et al., 2020)

* This paper focuses on the method to simulate disease aggregation levels using a random walker model, with information from longitudinal brain MRI and network-based statistics
* Each patients' simulated aggregation levels were added as a data modality in the network proposed by (van der Burgh et al., 2017)
* Including aggregation levels improved the accuracy of the multimodal model
* Showing how disparate data sources might be useful in prognosis prediction for ALS

**Cox model for spinal cord atrophy**

(Querin et al., 2017)

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* Atrophy at multiple points in the spinal cord was associated with faster disease progression

Fusilli section: data fusion background

(Cui et al., 2022)

**Why multimodal?**

* Using multiple types of data might reduce the bias in one particular modality if it’s balanced out by other data, for example education level on cognitive tests
  + disease stage has unknown benefit to patients

# Bibliography

Automatic citation updates are disabled. To see the bibliography, click Refresh in the Zotero tab.