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# Neuroimaging Techniques for Monitoring and Diagnosing Amyotrophic Lateral Sclerosis: Current Applications of AI and Emerging Innovations

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**ABSTRACT**

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by degeneration of upper and lower motor neurons, leading to muscle weakness, paralysis, and ultimately respiratory failure. Motor neurons are specialized nerve cells that control voluntary muscle movement and are located in the motor cortex of the brain, the brainstem, and the spinal cord. As these neurons deteriorate, the brain progressively loses its ability to communicate with skeletal muscles, producing the hallmark motor symptoms of ALS. Although the biological mechanisms underlying ALS are not yet fully understood, research has implicated several contributing processes, including mitochondrial dysfunction, glutamate excitotoxicity, oxidative stress, and neuroinflammation.

Neuroimaging techniques such as magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), functional MRI (fMRI), and positron emission tomography (PET) have increasingly been used to identify structural, functional, and metabolic changes associated with ALS, often preceding overt clinical decline. This report summarizes recent developments in the application of artificial intelligence (AI) and machine learning (ML) methods to ALS neuroimaging. Rather than presenting an exhaustive review, we focus on representative studies that illustrate how computational models are applied to neuroimaging data for disease classification, biomarker identification, and assessment of disease progression. Relevant literature was identified through targeted searches of PubMed.

Across imaging modalities, AI-based approaches have demonstrated the ability to detect ALS-related patterns that may be difficult to identify using conventional visual or statistical analyses. Studies most commonly employ support vector machines, random forests, and deep learning architectures applied to MRI and DTI features, with reported improvements in classification performance. However, many studies remain limited by small sample sizes, diverse imaging protocols, limited availability of control data, and challenges related to model interpretability and clinical validation.

Overall, AI-assisted analysis of neuroimaging data represents a rapidly evolving area of ALS research. Continued progress will depend on improved data sharing, standardized imaging pipelines, and validation across diverse patient cohorts before these approaches can be reliably integrated into clinical practice.

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## 1. INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disorder that primarily affects the motor system, leading to muscle weakness, paralysis, and eventually respiratory failure. The disease is characterized by the degeneration of upper and lower motor neurons, which are responsible for controlling voluntary muscle movement. These neurons are located in the motor cortex of the brain, the brainstem, and the spinal cord, and their progressive loss results in the hallmark motor symptoms of ALS[1].

Although ALS is traditionally considered a motor neuron disease, growing evidence suggests that it can also involve additional regions outside of the motor cortex, which may contribute to cognitive, behavioral, and sensory changes in some patients[2]. While the exact biological processes that cause and drive ALS remain incompletely understood, research has implicated multiple contributing mechanisms including mitochondrial dysfunction, glutamate excitotoxicity, oxidative stress, and neuroinflammation[3]. ALS affects approximately 4 to 6 individuals per 100,000 worldwide, and the global burden of the disease is projected to increase substantially over the coming decades[4,5].

Despite significant advances in neuroscience research and neurological care over the past three decades, roughly 90 to 95% of ALS cases occur without a known family history, while approximately 5–10% are considered familial. Familial ALS is most commonly associated with mutations in genes such as C9orf72, SOD1, TARDBP, or FUS[6]. It is important to note that there is still no curative treatment for ALS. Available therapies are limited to slowing progression and extending survival, and current data shows that these improvements are modest even in best case scenarios[7].

Diagnosis of ALS is typically made through exclusion, a lengthy and uncertain process that often takes up to 12 months from symptom onset[8]. In clinical settings, this time delay is crucial. By the time a definitive diagnosis is made, much of the early therapeutic window has passed, leading to motor and functional loss that might have otherwise been delayed or potentially avoided[9]. Thus, the early and accurate identification of ALS carries significant potential implications. Earlier diagnosis has the potential to improve patient outcomes by enabling earlier pharmacologic intervention and supportive care, facilitate enrollment in clinical trials, and accelerate the search for treatments. Additionally, studying patients in earlier stages of ALS could reveal novel mechanistic findings that would otherwise remain masked by neurodegeneration.

Given the complexity and time sensitivity of ALS care, neuroimaging has emerged as a cornerstone in evaluation, prognosis, and epidemiological research[10]. Structural magnetic resonance imaging (MRI) is routinely used in the diagnostic workup of ALS, primarily as a way to assess cortical and subcortical atrophy while also ruling out alternative pathologies[11]. Beyond structural imaging, functional modalities including diffusion tensor imaging (DTI) and functional MRI (fMRI) reveal corticospinal tract (CST) degeneration and disrupted brain network connectivity[12,13]. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) complement these modalities by detecting metabolic abnormalities and inflammation. Often used together in clinical practice, these neuroimaging tools and others have advanced the understanding and visualization of ALS[14]. By harnessing these unique physiological data, it is possible to shift from a purely symptom-based view towards a broader understanding of ALS and its effects on overall central nervous system architecture.

However, interpreting the vast amount of data produced by these modalities remains a major obstacle for both clinicians and researchers alike. Traditional statistical analyses often struggle with multidimensional, noisy datasets where subtle ALS-specific patterns may be hidden. Extracting meaningful, reliable, and accurate insights from such complex data requires reproducible analytical approaches capable of modeling nonlinear and multivariate relationships. With this comes additional manpower, time, and healthcare resources which are often not available, especially in non-academic clinical centers. ML and artificial intelligence AI techniques have emerged as a potential solution to this challenge[15]. By identifying complex relationships across large amounts of imaging and clinical data, ML models have shown potential to distinguish ALS from controls[16,17]. Similarly, work is underway to harness these algorithmic capabilities to estimate disease progression and predict therapeutic responses. Studies employing AI and ML models, including random forests (RF), support-vector machines (SVM), and ensemble models (EM) have shown promising accuracy in patient classification and prognostication[18,19,20]. Deep learning architectures such as convolutional neural networks (CNNs) and vision transformers (VTs) further enhance performance by autonomously learning these ALS-specific spatial features from imaging data[21,22].

Despite these recent advances, the field still faces considerable limitations including small sample sizes, access to control data, lack of standardized imaging protocols, and the risk of overfitting in models trained on limited data[23]. Additionally, there are numerous ethical challenges such as patient confidentiality, transparency in model development, and equitable access to AI-assisted care[24]. Nevertheless, ongoing efforts by multicenter groups are actively attempting to address these challenges. This review aims to synthesize recent advances in neuroimaging and ML applications in ALS, highlighting available data sources, current AI and ML models under evaluation, and key methodological challenges as these technologies continue to grow in clinical application.

## 2. CURRENT NEUROIMAGING TECHNIQUES IN ALS

Given the complex and heterogeneous pathology of ALS, clinicians and researchers rely on combining multiple neuroimaging modalities to characterize structural, functional, and metabolic alterations associated with ALS[25]. These modalities complement one another by capturing separate yet related aspects of neurodegeneration in ALS, ranging from cortical atrophy and white-matter disruption to altered connectivity and metabolism. Interpretation of these findings typically involves multidisciplinary input from neurologists, neuroradiologists, and imaging scientists who help develop and implement these protocols.

Of all available neuroimaging modalities, MRI remains the most widely used in both clinical and research settings. MRI uses a strong magnetic field and radiofrequency pulses to detect signals from hydrogen protons in the body, allowing detailed images of soft tissues to be generated based on how these protons behave in different biological environments. In the context of ALS, MRI is commonly used to exclude conditions that can mimic ALS, such as cervical myelopathy or multiple sclerosis, and to evaluate patterns of brain and spinal cord atrophy, particularly in the precentral gyrus and along the corticospinal tracts[26].

MRI is especially useful for visualizing gray and white matter. Gray matter primarily consists of neuronal cell bodies, dendrites, and synapses, while white matter is composed mainly of myelinated axons that connect different brain regions[27]. In ALS (as well as other neurodegenerative diseases), degeneration of motor neurons and their projections often leads to tissue loss, which can appear on MRI as cortical thinning and enlargement of surrounding spaces[28]. MRI commonly uses two major image sequence protocols, also termed "contrasts": T1-weighted and T2-weighted sequences. T1-weighted imaging highlights anatomical structures and tissue composition and is often used to assess cortical thickness and atrophy. In ALS, T1-weighted scans are most commonly used to asses thinning of the motor cortex, which may correspond to a patient's decline in mobility. T2-weighted and FLAIR (a modified T2) sequences are sensitive to water content and tissue injury and are commonly used to detect signal abnormalities. In ALS, these sequences may show hyperintensity along the corticospinal tracts and brainstem, reflecting upper motor neuron involvement[29,30,31].

In practical terms, MRI serves as the workhorse for ALS imaging, and neuroimaging as a whole. It is already embedded into routine clinical workflows, accessible in most hospitals, and provides meaningful diagnostic information without the need for advanced post-processing or specialized data sharing pipelines. For many centers, particularly those outside large research institutions, MRI serves as the most feasible tool for neuroimaging.

DTI is a more recent and advanced MRI technique that quantifies the movement of water molecules along white-matter tracts, which provides measures of axonal integrity and connectivity[32]. DTI captures how water moves through the brain's wiring. In healthy tissue, water tends to flow along organized axonal pathways, but in ALS, the breakdown of these fibers causes water to spread more randomly[33,26]. These alterations can extend beyond the motor cortex, supporting the concept of ALS as a multisystem disorder affecting both motor and non-motor networks[34,35,36]. Because of its sensitivity to early structural changes, DTI is viewed as a promising tool for detecting early stage disease progression, again highlighting the importance of early neuroimaging analysis in ALS.

Magnetic resonance spectroscopy (MRS) provides a noninvasive way to measure biochemical changes in the brain that standard MRI cannot capture. Using the same scanner hardware as structural MRI, proton MRS detects signals from key metabolites that reflect the health of neurons and glial cells. In ALS, decreased N-acetylaspartate indicates neuronal loss, while elevated myo-inositol and choline suggest glial cell activation and cell membrane breakdown[37,38,39]. Although MRS remains primarily a research tool, its ability to detect early biochemical changes highlights its potential as a valuable ALS biomarker detection tool.

FMRI is a type of neuroimaging that measures brain activity by detecting changes in blood flow via the blood oxygen level dependence (BOLD) signal[40]. It allows researchers to visualize and quantify which parts of the brain display increased neuronal activity, either at rest or during assigned tasks. In ALS, fMRI reveals altered connectivity within motor regions, including the primary motor cortex and supplementary motor area, as well as non-motor areas such as the prefrontal and parietal cortices[41]. These changes are thought to emerge before clinical symptoms present, suggesting that fMRI can detect early network disruption[13]. Beyond diagnosis, fMRI may offer a valuable way of tracking disease progression and therapeutic response, complementing structural and metabolic imaging with a functional connectivity datapoint.

PET provides a way to quantify the metabolic activity of the brain. By using small amounts of radiolabeled tracers, PET scans highlight areas of atypical neuronal glucose metabolism. In ALS, PET commonly shows reduced metabolism in the motor and premotor cortices and increased activity in regions such as the brainstem, cerebellum, and limbic system, patterns thought to reflect both degeneration and compensatory reorganization[26,42,14]. PET tracers targeting specific proteins also allow visualization of microglial activation, offering a unique in-vivo marker of neuroinflammation and disease progression[43,44]. SPECT provides complementary information about cerebral perfusion and functional integrity. Using gamma-emitting tracers such as $[^{99m}Tc]$-HMPAO or $[^{99m}Tc]$-ECD, SPECT studies in ALS have demonstrated reduced blood flow in the motor cortex and frontal lobes, changes that are thought to occur prior to visible structural atrophy[42,14]. Together, PET and SPECT provide a unique link between neural degeneration, metabolic activity, and vascular health in ALS detection and monitoring.

## 3. AI AND MACHINE IN ALS NEUROIMAGING

Neuroimaging findings in ALS are often subtle, scattered across different anatomical regions, and variable between patients and imaging centers. As a result, consistent interpretation using conventional visual inspection and statistical methods can be challenging. As a result, AI and ML approaches have been increasingly applied to ALS neuroimaging to help identify complex patterns within large imaging datasets and to help support clinical analysis.

Across current studies, AI methods in ALS neuroimaging are generally applied to several major task categories. These include *classification*, such as distinguishing ALS patients from healthy controls or other neurological disorders; *segmentation*, which involves automatically identifying and measuring brain regions of interest; *biomarker discovery*, aimed at detecting imaging features associated with disease presence or progression; *phenotyping and subtype discovery*, which aims to identify distinct imaging patterns within ALS populations; and *prognosis*, which attempts to predict the severity of functional decline and other ALS symptoms. Framing AI applications around these task-level goals is helpful when assessing how different approaches are being used and what clinical goal they accomplish.

Many of these tasks build on the ability of neuroimaging techniques to detect ALS-related structural and functional changes, including gray- and white-matter degeneration and altered network activity. With the exception of convolutional neural networks and normative autoencoders, most ML models operate on quantitative features extracted from imaging data, such as regional cortical thickness, gray matter volume, fractional anisotropy, mean diffusivity, and measures of corticospinal tract integrity. Because ALS primarily affects the motor system, atrophy and structural changes are most often observed in the primary motor cortex, supplementary motor areas, and corticospinal tracts, making these regions especially important for AI-based biomarker development. Moreover, examining how AI models detect disease-related patterns may also contribute to improved understanding of the pathology underlying ALS itself[23].

Machine learning methods are particularly well suited for distinguishing ALS-affected brains from healthy controls. Among the wide range of available approaches, support vector machines (SVMs) and random forests (RFs) are among the most frequently used in ALS neuroimaging studies, in part due to their strong performance with relatively small datasets.

When examining the currently available studies, the implementation of AI generally follows a similar process. It typically begins with the selection of a specific machine-learning algorithm or model architecture, with different approaches designed to handle different data types, each requiring distinct preprocessing and training strategies[45]. Researchers generally look at what type of data the models can handle, their accuracy, and most importantly specialty.

The application of AI in PET imaging enhances the accuracy of image reconstruction, noise reduction, and biomarker quantification in ALS research. ML algorithms can analyze large amounts of data to detect metabolic dysfunction, neuroinflammation, glutamate dysregulation, and hypometabolism in key brain areas like the motor cortex, all being key hallmarks of ALS. Similarly, in SPECT, ML can identify early signs of reduced blood flow and recognize characteristic perfusion patterns in the motor cortex and frontal lobes. Despite these capabilities, AI-driven functional neuroimaging in ALS remains far less common than its structural counterpart.

**Training**

Within supervised ML models, when classifying given values many models utilize a system of weights specifying how much a trait might affect the outcome[46]. For example, when observing Fractional Anisotropy values it is evident certain values attribute to greater chance of a patient possessing ALS. This finding results in models giving greater influence or weight to said values. In contrast, the farther the FA value deviates from the ideal range associated with ALS, the fewer influence it has on the network's prediction; at extreme values, it decreases the estimated probability of the brain being classified as ALS. The model modifies the weight and biases through a process known as backpropagation where the model after identifying its outcome tries to maximize the weights applied to the brain to get as close as the desired outcome. By reviewing large amounts of data the model can perfect the weights however this would take hundreds of samples. While the above process may be the norm, many variations or completely unique training systems could be found in different models, specifically within the Classical ML models.

**Specialty**

Different AI and machine learning models are designed for different types of problems, and selecting an appropriate model is essential to maximizing performance. This involves understanding each model's strengths and limitations. For example, linear regression is not suitable for classification tasks because its outputs are unbounded, while logistic regression is specifically designed for classification problems. Specialty also involves considering factors such as computational efficiency, robustness to high-dimensional data, and the ability to adapt to small datasets, which are common challenges in neuroimaging research. To address these issues, researchers increasingly combine specialized models with optimized data handling techniques, such as using tabular features extracted from neuroimaging data to improve performance while managing dataset size and complexity.

**Deep Learning Approaches**

Deep learning refers to neural networks or ML models designed to loosely mimic how biological neural systems process information. These models have been increasingly applied in clinical settings and ALS research, which have shown promise for tasks such as survival prediction, disease classification, and diagnostic support. Their general archetype contains an input layer, output layer, and a certain number of hidden layers. When processing information data, such as images, text, or signals, enters the model with each input and feature being assigned a node. For example, in image analysis, each pixel intensity is represented as a number, forming a multidimensional array. However, in language models, words are converted into numerical embeddings that capture syntactic and semantic relationships. The neuron then applies the respective weights that it learned from training to determine how much that neuron should affect the outcome. For however many hidden layers there are, this process would repeat until the signal reaches the output layer, which uses the final processed values to produce the network's prediction for the given input[47]**.** Generally, additional layers allow models to learn more abstract patterns and capture hierarchical features with such models being termed deep neural networks (DNN).

From there, different types of models branch off. Feedforward Neural Networks (FNNs), also called Multilayer Perceptrons (MLPs), pass data in one direction from input to output through fully connected layers. They work well for structured or tabular data but don't naturally handle sequential or spatial relationships. CNNs, which are commonly used in ALS neuroimaging studies, use convolutional layers to detect spatial hierarchies in data, making them particularly well suited for medical image analysis, use convolutional layers to pick up on spatial hierarchies, making them especially good for image analysis. VTs offer another variation for image data by dividing images into patches and encoding them into token sequences with positional embeddings to retain spatial information. Self-attention layers then analyze the relationships between all patches, capturing long-range dependencies and global context. Recurrent Neural Networks (RNNs), on the other hand, are designed for sequential or time-series data, keeping a hidden state that carries information from previous inputs so they can learn temporal patterns. Normative diffusion autoencoders are similar to CNNs in that they can directly analyze imaging data; however, they are designed for a different purpose. They are trained specifically on healthy control data to learn typical patterns. Instead of predicting an output, they reconstruct the input, and during testing, errors in reconstruction reveal abnormalities, making them effective for identifying outliers or pathological changes.

To support ALS diagnosis and biomarker discovery, artificial neural networks (ANNs) have been increasingly applied to neuroimaging data, as they are well suited for identifying complex and distributed patterns associated with neurodegeneration. In one study, a DNN was trained on 135 subjects using T1-weighted and T2-weighted MRI, as well as DTI targeting white matter[19]**.** The model was trained separately on clinical characteristics, brain morphology, and MRI data. Each individual model achieved 60–70% accuracy; however, when these inputs were combined, performance increased to 84%, demonstrating improved accuracy in identifying ALS when multimodal features were integrated. This approach revealed significant hypothalamic atrophy in ALS patients compared to controls, confirming that volumetric measurements derived from deep learning can be directly traced back to ALS-related neurodegeneration and serve as a reliable marker for distinguishing patient groups.

Due to the presence of neurological decline in both normal aging and other neurodegenerative disorders, it can be hypothesized that effective ALS diagnosis requires models that can identify features uniquely attributable to ALS rather than general neurodegeneration. In this context, DNN is likely well suited because the input data are multifaceted and high-dimensional, incorporating complex MRI-derived and clinical variables with nonlinear interactions.In studies such as this one, where predictive signal emerges from coordinated interactions across multiple brain regions rather than isolated features, DNNs are particularly effective. This is especially relevant in ALS, which disrupts distributed motor and extramotor networks rather than a single anatomical site[2]. DNNs are therefore well suited to modeling network-level degeneration patterns that reflect the systems-level biology of the disease.

In another study, CNNs were applied to T1-weighted MRI for automated hypothalamus segmentation and volume quantification[48]**.** The hypothalamus is of particular interest in ALS because it plays a central role in regulating metabolism, autonomic function, sleep, and endocrine signaling, all of which are increasingly recognized as being disrupted in ALS beyond classical motor symptoms[48]. However, due to its small size, deep location, and irregular boundaries, the hypothalamus is difficult to measure reliably using manual or traditional image-processing techniques[48]. By using CNN-based automated segmentation, Vernikouskaya et al. were able to precisely isolate the hypothalamus and quantify subtle volume changes across large datasets. This approach revealed significant hypothalamic atrophy in ALS patients compared to controls, providing direct biological evidence that non-motor regulatory centers are involved in ALS-related neurodegeneration. Importantly, AI-enabled segmentation allows investigators to examine structures that were previously difficult to study at scale, opening new avenues for understanding multisystem involvement in ALS.

**Classical Approaches**

Classical ML models are algorithms that learn patterns from labeled or unlabeled data to make predictions or find structure. Unlike deep learning models, they typically do not involve multiple layers of neurons or complex hierarchical feature extraction. Instead, they rely on explicit mathematical rules or decision-making structures to map input features to outputs. Supervised models, like SVM or RF, learn from labeled data by finding patterns that separate or predict target outcomes, often using concepts like distances, splits, or voting mechanisms. Indeed, SVMs identify the boundary that best separates different classes while maximizing the margin between them, and for data that is not easily separable, they use kernel functions to project inputs into higher-dimensional spaces. RFs take a different approach, combining multiple decision trees, each trained on random subsets of the data and features. Each tree makes its own prediction, and the results are aggregated through majority voting for classification or averaging for regression.

Classical ML approaches remain popular in ALS neuroimaging, particularly SVMs and RFs, which have been applied to MRI and DTI scans to detect biologically meaningful ALS features, including degeneration of the corticospinal tracts and gray matter loss within motor and premotor cortices. One study used SVMs to analyze DTI images and successfully distinguished ALS patients from health controls with over 83% accuracy[16] using said white matter properties, indicating its potential for clinical application in ALS diagnosis. The model started extracting features from the DTI images, scoring and ranking the features in order of importance in identifying ALS.

Another instance of Classical ML is a study using RF to classify different ALS phenotypes with 70-90% accuracy[49]. This study observed over 100 white matter attributes and 10 grey matter attributes which it then fed to a RF classifier to identify if the sample was from one of four phenotypes. It looked at 91 ALS patients and 15 controls screened using both MRI and DTI. The study tested ANN, Normal decision trees, and RF, with RF achieving the highest accuracy. This increased performance is likely due to the moderate sample size and high-dimensional data, conditions where methods such as RF tend to perform well. In contrast, ANNs typically require much larger datasets to learn stable patterns, and are more prone to overfitting when the number of features is high relative to the number of subjects.

**Unsupervised Learning**

In supervised learning models, the algorithm learns from pre-labeled examples laid out by the human developer. In contrast, unsupervised learning models are given only raw data and must organize it into meaningful groups or patterns, assigning new data to these groups later. For example, clustering algorithms like K-Means move cluster centers to group similar points, and dimension-reducing PCA algorithms find directions that capture the most variation. Neural network-based models, like autoencoders, adjust weights to recreate the input data. Through this process, unsupervised models learn the underlying structure of the data without any labels. For example, grouping structural brain scans into groups based on shared features such as white matter volume.

Although the literature is sparse on the use of unsupervised learning models, this field has the potential to highlight new ALS subtypes or predict disease severity, even if the data is not perfectly organized. With the limited amount of training data and available datasets unsupervised learning may be key to finding a reliable solution. One of the main advantages is a very low chance of overfitting and bias - A utility that would be especially useful in clinical contexts where data organization and prep-processing may be limited. Unsupervised learning has increasingly been applied in neuroimaging studies, including those focused on ALS.

In this study, 387 ALS patients (mean age 62, balanced across sexes) underwent T1-weighted MRI, and an unsupervised clustering model was used to analyze structural changes across 15 brain regions. The model achieved a silhouette coefficient of 0.572 in distinguishing two distinct anatomical subtypes: one with predominant frontotemporal involvement and another with more widespread cortical and subcortical changes. These clusters align with known clinical heterogeneity in ALS, demonstrating that MRI-driven ML can both capture disease-related atrophy patterns and reliably trace them back to ALS-specific neurodegeneration[50]. Unsupervised clustering allows models to identify natural similarities and differences in brain structure without relying on predefined labels. In this study, this approach enabled the grouping of ALS brains based on volumetric patterns and the specific regions affected by the disease. Although interpretability remains a challenge, unsupervised learning offers a powerful way to uncover previously unrecognized disease subtypes and patterns of neurodegeneration.

**Summary of Key models and Results**

A common pattern appears when observing models used amongst neuroimaging ALS papers being that most papers prefer SVM and RF. This can be attributed to the small datasets in ALS specifically with neuroimaging in which RF and SVMs excel. In particular SVMs are popular as neuroimaging is found with noise which SVMs are capable of dealing with. RFs in addition to handling small datasets are easily interpretable and are good at dealing with mixed modalities. However with the arrival of new larger datasets in ALS and more refining within deep learning neural networks still remain and are emerging as a new promising model to use as classifiers and model regression.

Another prevalent pattern is the modality chosen to research with the most common being MRI and DTI. MRI seems to be a favorite most likely due to their accessibility and popular use due to little invasiveness. These modalities are designed to measure and display degeneration in the brain. Specifically ALS targets grey matter and white matter. However, PET potentially can be used for earlier intervention as the field continues to progress due to metabolic changes appearing earlier than structural changes. In table 1, a summary of models is presented, as well as their key variables.

**Table 1: ML Models Used in ALS Neuroimaging**

| Study | Model | Modality | Task | Sample Size | Biomarker / Input | Performance | Key Findings |
|---|---|---|---|---|---|---|---|

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| D'hulst et al., 2018; *ALS Frontotemporal Degener.*; PMID: 29862846 | SVM (Trained on Italian subjects) | PET | ALS identification | Fed 195 subjects; 40 controls | FDG-PET metabolic maps | Could not differentiate between controls and ALS | This multicenter study confirms that the 18F-FDG ALS pattern is stable across centers. However, it highlights the importance of carefully selected controls, as subclinical frontal changes might be present in patients in an oncological setting. Although ALS-associated imaging patterns were reproducible across centers, robust effectiveness requires stability and predictable contrast in both ALS and control cohorts. |
| | SVM (Trained on Belgian subjects) | | ALS identification | Fed 175 subjects; 20 controls | FDG-PET metabolic maps | 94.8% accuracy in identifying ALS brains<br><br>12.5% accuracy in identifying control | |
| Van Weehaeghe et al., 2016; *J Nucl Med*; PMID: 26940764 | Discriminant Analysis | PET | Prospective ALS classification | 135 subjects; 20 controls | VOI metabolic metrics | 88.8% (VOI discriminant) | VOI discriminant analysis validated prospectively; SVM performed well under strict selection. |
| | SVM | | | | | 100% (SVM under strict criteria) | |
| Thome et al., 2022; *Human Brain Mapping*; PMID: 34655259 | Random Forest | MRI/ rs-fMRI | ALS vs. control classification | 97 ALS; 59 controls | Brain volumes; functional connectivity; RNN-derived features | Up to 66.82% | Multimodal models (volume + dynamic connectivity) outperformed unimodal; rs-fMRI connectivity was strongly predictive. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Chen et al., 2020; *Front Neurol.*; PMID: 32411072 | SVM | DTI | ALS vs. control classification | 22 ALS; 26 controls | Voxel-wise FA | ~83%<br><br>AUC 0.862 | Voxel-wise DTI FA features supported accurate ALS discrimination. |
| Bede et al., 2022; *J Neurol Sci.*; PMID: 34875472 | MLP | MRI/ DTI | ALS vs. PLS vs. poliomyelitis mimic classification | N/A | Cortical thickness; subcortical volumes | 93.7% Poor diagnostic accuracy for PLS: 43.8% and poliomyelitis 60% | MLP successfully separated ALS from other motor neuron disease presentations. |
| Schuster et al., 2016; *PLOS ONE*; PMID: 27907080 | Logistic Regression (ridge) | MRI/DTI | ALS vs. control classification | 102 Subjects 81 Controls | Disease-specific VBM + DTI features | 78.4% accuracy; 80% sensitivity | MRI features in a logistic model distinguished ALS from controls with reasonable accuracy. |
| Kocar et al., 2021; *Front Neurol.*; PMID: 34867726 | SVM(Verified using MLP/Neural Network) | MRI/DTi | ALS vs. control classification | 404 Subjects 98 Controls | FA & texture features | AUC ≈ 0.9 | Demonstrated the power of ML in the application of multiparametric quantitative neuroimaging data to ALS. |
| Behler et al., 2023; *Int J Mol Sci* (Review); PMID: 36768231 | Review (SVM/ RF summarized) | MRI/DTI | Biomarker & ML review | N/A | Various DTI metrics | N/A | A synthesis of ML approaches applied to DTI in the context of ALS biomarker development. |
| Rajagopalan et al., 2023; *Diagnostics*; PMID: 37174914 | Random Forest | MRI | ALS phenotyping/subtype | 91 subjects | White and Grey Matter Attributes, | 70–94% (depending on class) | RF on graph features successfully separates ALS phenotypes including ALS-FTD. |

## 4. OVERVIEW OF ALS NEUROIMAGING DATASETS

Beyond algorithm selection, the availability and quality of neuroimaging datasets play a pivotal role in the development and performance of ML models in ALS research. Dataset characteristics such as subject size, quality, and demographic diversity directly influence model robustness, generalizability, and susceptibility to bias[51]. In the context of ALS, where clinical heterogeneity is significant, neuroimaging datasets that include participants across a broad range of ages, sexes, and ethnic backgrounds are essential for identifying disease-related patterns that extend beyond a single subgroup[52].

Larger and more diverse imaging cohorts allow ML models to capture the diversity of ALS-related neurodegeneration while reducing the risk of overfitting, especially to site-specific or demographic features. Variability within training data also improves model performance on previously unseen data, an essential requirement for clinical translation. However, despite growing interest in ALS neuroimaging, the number of openly accessible datasets remains limited. Many existing ALS datasets prioritize genetic or clinical variables, with relatively fewer incorporating multimodal neuroimaging data. As a result, ALS-focused ML studies frequently rely on small cohorts or restricted-access datasets, which limits external validation and reproducibility.

To illustrate the current landscape of ALS neuroimaging data, Table 2 summarizes representative datasets that have been used in recent research or are publicly available through platforms such as OpenNeuro. These datasets were identified through targeted searches of PubMed using terms including “ALS Imaging”, “ALS Neuroimaging”, “ALS Dataset” “ALS Radiology,”, “ALS MRI”, “ALS PET”, “ALS fMRI”, “ALS Artificial Intelligence". and “ALS Machine Learning”, and were selected based on relevance to imaging-based ML applications.

In addition to ALS patient data, the inclusion of appropriate control datasets is essential for effective model training and evaluation. Control data can establish a baseline for normal anatomical and functional variability, enabling ML models to distinguish disease-related features from background noise[53]. Poorly matched control groups increase the risk of false-positive classifications and biased predictions, particularly when models inadvertently learn dataset-specific artifacts rather than disease-relevant patterns. Improper training strategies may further promote overfitting, resulting in models that perform well on training data but fail to generalize to independent cohorts[23]**.**

**Table 2: Key ALS Datasets**

| **Dataset Name and Link** | **Modality** | **Availability** | **Sample Size (including demographics)** |
|---|---|---|---|
| An fMRI Dataset for Appetite Neural Correlates in | fMRI | Open | 67 ALS subjects |

| | | | |
|---|---|---|---|
| People Living with Motor Neuron Disease | | | |
| Intra- and inter-scanner reliability of RS-fMRI BOLD and ASL with eyes closed vs. eyes open | fMRI | Open | 21 ALS subjects |
| Neuroimaging Endpoints in Amyotrophic Lateral Sclerosis | DTI | Available Upon Request | 24 ALS subjects |
| Data from: A prospective harmonized multicentre DTI study of cerebral white matter degeneration in ALS | DTI | Open | 66 ALS subjects; 23 controls |
| Canadian ALS Neuroimaging Consortium (CALSNIC) | MRI/DTI | Available Upon Request | Over 700 subjects and controls |
| Thalamic nuclei in motor neuron disease: volumetric profiles | MRI | Open | 100 ALS subjects; 117 controls |
| Deep learning predictions of survival based on MRI in amyotrophic lateral sclerosis | MRI | Available Upon Request | 135 ALS subjects |
| Human ALS MRI-Histology | MRI | Available Upon Request | 12 ALS subjects; 3 controls |
| A multimodal longitudinal study of structural brain involvement in amyotrophic lateral sclerosis | MRI | Open | 292 ALS subjects; 156 controls |

**Table 3: Key Normal Control Datasets**

| Dataset Name and Link | Modality | Availability | Sample Size (Number, sex, age) |
|---|---|---|---|
| The Dallas Lifespan Brain Study | MRI/PET | Open | 464 subjects |
| Longitudinal Multimodal Neuroimaging, Clinical, and Cognitive Dataset for Normal Aging and Alzheimer's Disease | MRI/PET | Available Upon Request | 755 subjects |
| Longitudinal Multimodal Neuroimaging, Clinical, and Cognitive Dataset for Normal Aging and Alzheimer's Disease | MRI, PET, DTI | Available Upon Request | 1379 subjects |
| UK BioBank | fMRI, MRI | Available Upon Request | fMRI: 94,930 subjects<br>MRI: 190,018 subjects |
| Cambridge Centre for Ageing and Neuroscience | fMRI, | Available Upon | 100 subjects |

| | | | |
|---|---|---|---|
| | MRI | Request | |
| Adolescent Health and Development in Context | fMRI and MRI | Open | 391 subjects |
| International Neuroimaging Data Sharing Initiative | MRI | Open | 3907 subjects |
| Parkinson's Progression Markers Initiative | MRI | Available Upon Request | 574 subjects |

## 5. CHALLENGES AND FUTURE DIRECTIONS

Over the past decade, significant progress has been made in understanding ALS, including its diagnosis and prognosis. However, research has shown that there is significant variability in how ALS presents and progresses over time[54]**.** In the United States, the average time from the first symptom to ALS diagnosis confirmation is 12 months[55]. During this period, patients with ALS will often undergo three to four consultations with different healthcare providers before being evaluated by an ALS specialist and receiving a definitive diagnosis. Delays in diagnosis are partly due to the lack of disease-specific biomarkers, as many biomarkers associated with ALS are also present in other neurodegenerative disorders[56,57]. Thus, identifying biomarkers that are more specific to ALS is an important research priority, as earlier diagnosis may have the potential to provide more impactful clinical care, as well as increase patient eligibility for participation in clinical trials.

One promising approach to improve ALS detection and characterization is the integration of ML and AI with neuroimaging. This approach enables the identification of intricate patterns and associations within imaging data that may not be apparent through traditional analysis methods. As imaging datasets grow in size and complexity, similar data-driven strategies have been used in other clinical domains to demonstrate how large-scale analysis can advance disease understanding and support the development of new diagnostic approaches. An example of this can be seen in the UK Biobank's large-scale proteomics initiative, which demonstrates how integrating advanced analytics with expansive biomedical datasets can enhance disease understanding and support the development of novel diagnostic approaches[58].

Looking ahead, future AI and ML approaches are likely to incorporate non-imaging data in combination with neuroimaging. These data sources may include clinical records, laboratory values, other biomarker findings such as electroencephalography (EEG). Integrating multiple data sources may allow models to better capture the heterogeneity of ALS. Although outside the scope of the present review, emerging tools such as large language models (LLMs) may also contribute to future neurodegenerative disease research by facilitating large scale data organization and analysis.

Despite growing interest in AI-based methods for ALS research, several challenges must be addressed before these tools can be applied safely and reliably in clinical settings. A major limitation is the lack of large, high-quality standardized datasets. ALS is a rare disease with significant clinical variability, making data collection and synchronization challenging. Additionally, AI models that are trained on small or limited demographic datasets can reduce generalizability and introduce bias[20]. Models developed under these conditions may perform well on training data but fail to produce reliable results when applied to new patient populations[23].

Another important challenge is model interpretability. Many AI systems rely on complex neural networks that function as "black boxes," making it difficult for clinicians and patients to understand how predictions are generated[59]. This gap in interpretability reduces clinical trust and adds complexity to the validation process. Before AI tools can be integrated into routine ALS care, they must undergo rigorous clinical validation, a process that is often time-consuming and resource-intensive. Addressing these challenges will require improved data-sharing efforts, greater transparency in model design, increased funding, and validation across diverse patient cohorts.

Beyond brain-focused neuroimaging, the spinal cord represents an important and relatively underexplored target for ALS research. Although fewer imaging studies have focused on the spinal cord, existing work has identified significant ALS-related changes in this region[60,61]. Pathological involvement of the anterior horns and corticospinal tracts is an anatomical hallmark of ALS, and advances in spinal cord imaging have improved the ability to detect metabolic, sensory, and interneuron abnormalities associated with motor neuron disease[62]. Earlier limitations related to the spinal cord's small size, motion artifacts, and image distortion previously restricted its study[63]. Recent improvements in imaging techniques have reduced these challenges, enabling more reliable detection of disease-related atrophy[64]**.** Notably, spinal cord imaging has identified gray matter alterations in the cervical cord during early stages of ALS, suggesting potential value as a biomarker for early disease detection[60].

## 6. CONCLUSION

Despite advancements in treatment and disease management, ALS remains a devastating neurodegenerative disorder with many underlying biological mechanisms still poorly understood. Neuroimaging has become an increasingly valuable tool in ALS research by enabling the detection of structural, functional, and metabolic brain changes that may occur before the onset of clear clinical symptoms. Both structural and functional imaging modalities have contributed to earlier disease characterization and improved understanding of disease progression.

The introduction of AI and ML methods into clinical research has created new opportunities for analyzing complex neuroimaging data. These models have demonstrated the ability to process large imaging datasets across diverse patient populations more efficiently than traditional analytical approaches. Given the heterogeneity of ALS and the complexity of its neuroimaging findings, AI-based tools may provide valuable support for clinical interpretation and research analysis.

However, significant challenges remain. Limitations in dataset size and diversity, risks of overfitting, and potential sources of bias continue to restrict clinical applications of current models. Addressing these issues will require improved data-sharing efforts, multi-center collaboration, and continued refinement of methodological approaches. Despite these challenges, ongoing advances suggest that the combined use of ML techniques and neuroimaging has the potential to play an important role in future ALS research, diagnosis, and treatment.

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