



Feature selection from magnetic resonance imaging data in ALS: a systematic review

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Abstract

Background: With the advances in neuroimaging in amyotrophic lateral sclerosis (ALS), it has been speculated that multiparametric magnetic resonance imaging (MRI) is capable to contribute to early diagnosis. Machine learning (ML) can be regarded as the missing piece that allows for the useful integration of multiparametric MRI data into a diagnostic classifier. The major challenges in developing ML classifiers for ALS are limited data quantity and a suboptimal sample to feature ratio which can be addressed by sound feature selection.

Methods: We conducted a systematic review to collect MRI biomarkers that could be used as features by searching the online database PubMed for entries in the recent 4 years that contained cross-sectional neuroimaging data of subjects with ALS and an adequate control group. In addition to the qualitative synthesis, a semi-quantitative analysis was conducted for each MRI modality that indicated which brain regions were most commonly reported.

Results: Our search resulted in 151 studies with a total of 221 datasets. In summary, our findings highly resembled generally accepted neuropathological patterns of ALS, with degeneration of the motor cortex and the corticospinal tract, but also in frontal, temporal, and subcortical structures, consistent with the neuropathological four-stage model of the propagation of pTDP-43 in ALS.

Conclusions: These insights are discussed with respect to their potential for MRI feature selection for future ML-based neuroimaging classifiers in ALS. The integration of multiparametric MRI including DTI, volumetric, and texture data using ML may be the best approach to generate a diagnostic neuroimaging tool for ALS.

Keywords: amyotrophic lateral sclerosis, machine learning, magnetic resonance imaging, motor neuron disease, neurodegeneration, neuroimaging, systematic review

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects several brain regions in a distinctive propagation pattern, with emphasis on the motor neurons.¹ To diagnose ALS as early as possible is a task of high clinical relevance for the optimized patients' care and the opportunity to be enrolled in clinical trials. With advances in neuroimaging in neurodegenerative diseases like ALS,^{2,3} it has been speculated that cerebral magnetic resonance imaging (MRI) may be able to provide insights that support an early diagnosis. Multiparametric, quantitative MRI has been discussed as a way to

achieve a composite neuroimaging index.³ However, the amount of biomarkers, as well as their (non-linear) interactions, makes a straightforward approach likely unsuccessful. Machine learning (ML) might be the missing piece to integrate multiparametric MRI data into a useful classifier.⁴ In a classification problem, the ML model is presented with a dataset and the correct outcomes (supervised learning). By model-specific rules, the model is fit to the data to predict the outcome. The model that is created in this process can then be used to predict the outcome of new data, that is, in a diagnostic set-up, a given patient's data are used to predict the correct

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diagnosis. With advanced ML techniques, the promise for highly personalized medicine emerged. However, it was quickly realized that ML models in medicine could not outperform health professionals, even in favorable comparisons,⁵ so a more realistic approach may be to restrict ML to very specific tasks. One of these tasks is quantitative neuroimaging, supporting (qualitative) human visual inspection.

In ALS, several studies have incorporated ML in a diagnostic pursuit (for a review, see Grollemund *et al.*⁶). In an early approach using a linear support vector machine (SVM), independent component analysis (ICA) from resting-state functional MRI (rs-fMRI) data yielded 71% accurate classification.⁷ With a similar approach, but using a multiple kernel SVM on rs-fMRI data, a 87% accurate classification was achieved.⁸ However, there was no independent test sample, and overfitting might have occurred, that is, the model cannot be generalized because it fitted the training data too tightly. Using T1-weighted (T1w) and diffusion tensor imaging (DTI) data, various classification models achieved an accuracy of 78–90%,^{9–11} although high accuracy might have resulted from model overfitting, given that features were not defined *a priori* or samples were limited. By the use of ML classifiers on texture data gathered from the corticospinal tract, 70–80% accuracy was reported.¹² Interestingly, when re-training general image recognition models like ResNet or VCG-16, a 60–63% accuracy was still achieved.^{13,14} Although these results are promising, overfitting remains one of the main challenges in ML. One of the most important mechanisms behind overfitting is the sample to feature ratio (SFR) which is a general parameter that helps assessing how many features an ML model can process before overfitting or underfitting is likely to occur.⁶ As a general rule, 10–15 samples per feature have been proposed; however, modern ML algorithms may even work with lower numbers.¹⁵ To date, there are few databases that collect MR images from patients with ALS in a meaningful amount, and even those may not be able to establish a reasonable ML model without some preselection of MRI features. In 2016, Grolez *et al.* published a systematic review that provides a useful collection of ALS-specific neuroimaging biomarkers that could be used for feature selection.¹⁶ The current review updates this previous work by specifically addressing ML

models. To this end, we conducted a systematic review on neuroimaging in ALS, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁷ To this end, we reviewed all available studies over the previous 4 years (i.e. from 2017 onward) that could contribute to disease classification. We compiled these data into a comprehensive list of findings that can be used as features in an ML model.

Methods

Search strategy and study selection

The literature review and study selection were conducted in accordance with the PRISMA guidelines.¹⁷ In March, 2021, a systematic search was conducted on the online library PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>). The search queries were ALS AND MRI, ALS AND ‘magnetic resonance imaging’, ALS AND neuroimaging, ‘amyotrophic lateral sclerosis’ AND MRI, ‘amyotrophic lateral sclerosis’ AND ‘magnetic resonance imaging’, and ‘amyotrophic lateral sclerosis’ AND neuroimaging. Only publications that were listed after 1 January 2017 were considered for this review. Regarding prior publications, we refer to the systematic review by Grolez *et al.*¹⁶ and to the meta-analyses by Shen *et al.*¹⁸ and Gorges *et al.*¹⁹ Our search yielded 632 database entries. In a cross-reference search, additional 7 records were found for a total of 639. These records were carefully checked by an experienced reviewer for the following criteria: the studies had to be published in a peer-reviewed journal in the English language; only human studies with *in vivo* cranial MRI were considered; and there had to be a group of healthy control subjects or mimic disorders and a group of subjects with sporadic ALS, according to common diagnostic guidelines. Primary lateral sclerosis (PLS), progressive bulbar palsy (PBP), and pure lower motor neuron disease (LMND) were considered as ALS spectrum disorders and thus also included.^{3,20,21} There had to be cross-sectional data, and inferential statistics had to be conducted on these data. Solely longitudinal data or regression analyses were not considered, as these would not help distinguishing ALS from healthy controls. However, if there were appropriate data in Supplementary Material, these studies could still be included. From the 639 entries, 213

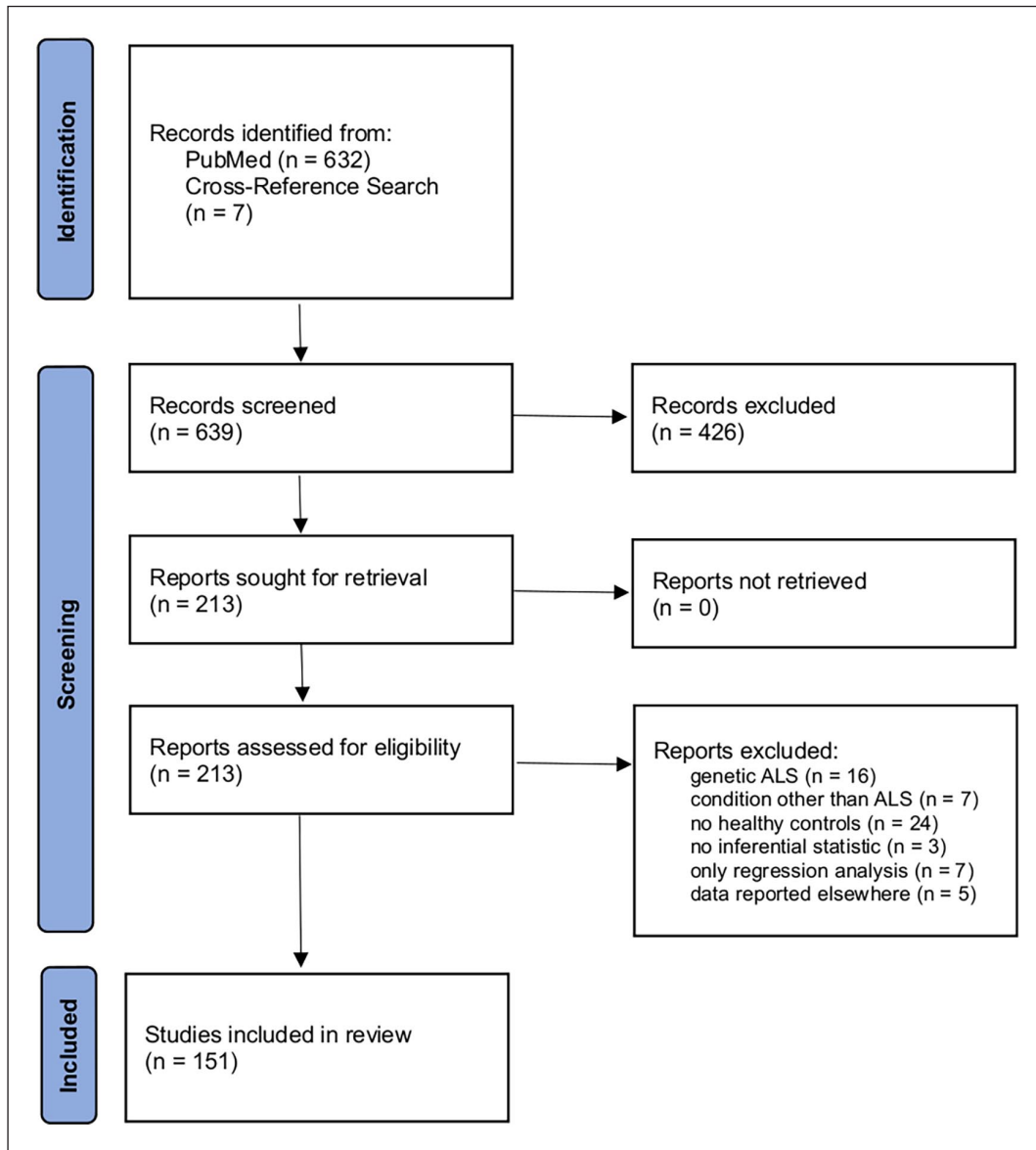


Figure 1. PRISMA flow diagram illustrating the literature review and study selection process.

reports were identified as eligible. In the full-text review, 62 reports were excluded due to the following exclusion criteria: genetic as opposed to sporadic ALS ($n=16$), no healthy control group ($n=24$), conditions other than ALS ($n=7$), no inferential statistics ($n=3$), only statistical regression ($n=7$), or data that were already reported elsewhere ($n=5$). In total, 151 studies were included in this systematic review. Figure 1 summarizes the literature review and study inclusion process according to the PRISMA guidelines. No automated tools were used in this systematic

review. Ethics approval and informed consent were not required for this systematic review.

Semi-quantitative analysis

During the full-text review, all data that could be used for disease classification in an ML model were noted, both from the report itself and from its Supplementary Material if provided. In a semi-quantitative synthesis, it was analyzed which brain areas were most commonly reported. This was done by counting how many studies reported a

brain region as a significant finding. We categorized these regions into ‘major’ and ‘minor’ findings, based upon the quantity of studies that reported each finding. This procedure was repeated for each MRI modality. The goal of this semi-quantitative analysis was to provide a comprehensive list of findings that could be used for disease classification in an ML model. As this approach relies solely on the quantity of reports, underreporting or overreporting of specific results can bias the analysis.

Results

There were several studies with data from different modalities; these data are reported separately for each of these modalities. From the 151 studies, a total of 221 datasets were analyzed. In addition, we provide a comprehensive summary of studies which included at least 50 subjects (ALS patients and controls combined) and statistical correction for multiple comparisons. A total of 129 datasets resulted, summarized in Tables 1–5.

Structural alterations: T1w imaging

Seventy-eight datasets of T1w imaging-based studies were reviewed (Table 1). In accordance with the previous literature,¹⁶ most studies reported loss of gray matter volume in the precentral gyrus,⁷² either by cortical thickness assessment or by voxel-based morphometry.³³ In addition, further areas were reported that resembled the pattern of the neuropathological four-stage model of the propagation of pTDP43 in ALS.¹⁰⁷ These areas included the frontal cortex, the anterior cingulate cortex, as well as subcortical and temporal structures, especially the thalamus, the hippocampus, and the amygdala, summarized in a recent controlled study with 292 participants with ALS.⁶⁸ Single studies with high numbers of participants described significant atrophy in the hypothalamus in patients with ALS, irrespective of the disease stage⁷⁰ and abnormal T1 signal in the tongue, with further findings in area and shape of the tongue.⁶⁹ Few studies conducted white matter morphometry with mixed results, showing abnormalities in sensorimotor and cerebellar tracts.⁷¹

Microstructural alterations: diffusion tensor imaging

Sixty-six datasets were reviewed for DTI data (Table 2). Overall, the analysis of fractional anisotropy (FA) revealed the most consistent results

when comparing different studies. A meta-analysis with a total of 3752 subjects found the following four tracts to be the most important: the corticospinal tract, the corticorubral/corticopontine tract, the corticostriatal tract, and the proximal portion of the perforant path, which have previously been described as stage-defining tracts (stages 1–4).^{19,86,87,108} A recent multicenter study replicated these findings, with additional abnormalities found in the frontal lobe.⁸⁸ Within the corticospinal tract, the posterior limb of the internal capsule, the corona radiata, and the cerebral peduncle were shown to be the most affected.⁸⁵ Of note, the application of the analysis approach neurite orientation and dispersion density imaging (NODDI) to ALS demonstrated axonal loss in the corticospinal tract to be the major contribution to altered diffusivity and also identified dendritic alterations within the precentral gyrus.¹⁰⁹ In addition to these stage-defining tracts, the corpus callosum has consistently been found to exhibit reduced FA, especially in the motor and premotor segments.^{76,110}

Functional alterations: resting-state functional magnetic resonance imaging

Twenty-three datasets were reviewed (Table 3). Overall, results were heterogeneous, with both increased and decreased functional connectivity in the pre- and postcentral gyri, the frontal and temporal lobes, the operculum, the insula, and the lingual gyrus.^{38,39} In a multicenter study with 173 patients with sporadic ALS and 79 healthy controls, increased functional connectivity in precentral, middle, and superior frontal areas in ALS and in the sensorimotor, basal ganglia, and temporal networks in PLS was reported.⁹³

Alterations in brain connectivity: connectomics

Eight datasets were reviewed (Table 3). As network parameters, only the global efficiency was consistently decreased in patients with ALS.⁹⁷ In addition, some studies found reduced nodal degree in the frontal lobe.^{75,97} In a multicenter study, decreased structural connectivity in sensorimotor, basal ganglia, frontal, and parietal areas was reported.⁹³ Of note, using a random walker model on connectivity data, a recent study simulated disease spreading that resembled propagation patterns in ALS, with additional survival prediction using deep learning.⁹⁴

Table 1. Summary of main structural/morphometric findings from studies with T1-weighted imaging data in ALS.

Publication	ALS	Controls	Main finding
Buhour <i>et al.</i> ²²	37	37	Gray matter atrophy in the right precentral gyrus, the left postcentral gyrus, the left paracentral lobule, the left inferior temporal gyrus, the left supramarginal gyrus, and the right putamen
Illán-Gala <i>et al.</i> ²³	31	37	Cortical thinning in the precentral gyrus, paracentral frontal regions, and the precuneus; in ALS with cognitive or behavioral symptoms: cortical thinning in frontoinsular and temporal regions
Cheng <i>et al.</i> ²⁴	60	60	White matter atrophy in the corticospinal tract
de Albuquerque <i>et al.</i> ²⁵	63	64	Gray matter atrophy in the precentral cortex and several frontal areas; cortical thinning in paracentral, precentral, and temporal areas
Schuster <i>et al.</i> ²⁶	60	69	Cortical thinning of the precentral and paracentral gyri contributes to survival prediction in ALS via binary logistic ridge regression
Shen <i>et al.</i> ²⁷	55	20	Gray matter atrophy in the frontal lobe, temporal lobe, precentral gyrus, cingulate gyrus, and the thalamus, most prominent in ALS-FTD
Hu <i>et al.</i> ²⁸	42	21	No significant difference in voxel-based morphometry between ALS with and without cognitive deficits
Dadar <i>et al.</i> ²⁹	66	42	Atrophy of the precentral gyrus, the corticospinal tract (including the internal capsule and brainstem), anterior cingulate cortex, and posterior parietal areas
Bede <i>et al.</i> ³⁰	48	50	Volume reduction in the basal ganglia; gray matter alterations of striatal subregions that project to rostral motor and executive cortical regions in ALS-FTD
Agosta <i>et al.</i> ³¹	67	22	Cortical thinning in the precentral gyrus and prefrontal, parietal, temporal, and occipital cortices
Branco <i>et al.</i> ³²	50	38	Atrophy of the amygdala in ALS with cognitive impairment
Kim <i>et al.</i> ³³	62	57	Lower gray matter density mostly in the precentral gyrus and adjacent pre- and postcentral regions, with more widespread frontotemporal involvement in bulbar ALS
Bede <i>et al.</i> ¹⁰	75	75	Precentral gyrus, thalamus, caudate, nucleus accumbens, hippocampus, and amygdala volume contribute to disease classification in a canonical discriminant analysis
Christidi <i>et al.</i> ³⁴	56	25	Gray matter atrophy in the pre- and postcentral gyri, frontal regions (especially in ALS with pathological laughing and crying), temporal regions, subcortical structures, and the left cerebellum
Acosta-Cabrero <i>et al.</i> ³⁵	28	39	No significant difference in subcortical volumetry, voxel-based morphometry, or cortical thickness analyses
Ogura <i>et al.</i> ³⁶	71	69	Gray matter volume reduction near the right parahippocampal gyrus and in the anterior part of the left temporal lobe, the latter related to semantic deficits in ALS
Trojsi <i>et al.</i> ³⁷	54	22	No significant difference in voxel-based morphometry
Trojsi <i>et al.</i> ³⁸	32	21	No significant difference in voxel-based morphometry

(Continued)

Table 1. (Continued)

Publication	ALS	Controls	Main finding
Qiu <i>et al.</i> ³⁹	60	60	Atrophy in the left precentral gyrus and increased gray matter volume in several cerebellar subregions, possibly as compensation
Gellersen <i>et al.</i> ⁴⁰	60	1471	Meta-analysis; cerebellar atrophy in the vermis (culmen and nodule), left posterior lobe, left inferior semi-lunar lobule, and bilateral anterior lobe
Qin <i>et al.</i> ⁴¹	28	28	Atrophy in the precentral gyrus, more widespread in late-stage ALS
Ferraro <i>et al.</i> ¹¹	123	78	Cortical thinning of the precentral gyrus contributes to disease classification in a random forest analysis
Consonni <i>et al.</i> ⁴²	48	26	Cortical thinning in frontoparietal regions; widespread thinning in inferior frontal, temporal, cingulate, and insular regions in ALS with cognitive impairment
Contarino <i>et al.</i> ⁴³	42	23	Cortical thinning in the precentral cortex and paracentral lobule
Bharti <i>et al.</i> ⁴⁴	71	56	No significant difference in gray matter volume in the cerebellum or its components
Chipika <i>et al.</i> ⁴⁵	133	117	Thalamic atrophy with the preferential involvement of nuclei mediating motor and cognitive functions
Machts <i>et al.</i> ⁴⁶	111	85	Progressive cortical thinning of the right parahippocampal gyrus; progressive hippocampal atrophy in ALS with memory impairment
Tu <i>et al.</i> ⁴⁷	20	31	Thalamic atrophy with deformation of the medial surface
Consonni <i>et al.</i> ⁴⁸	36	26	Cortical thinning in the right middle frontal sulcus and the right middle-posterior cingulate gyrus
Wirth <i>et al.</i> ⁴⁹	20	30	No significant difference in the cortical thickness of the pre- and postcentral gyrus
Chipika <i>et al.</i> ⁵⁰	88	117	Atrophy of the accessory basal nucleus and the cortical nucleus of the amygdala
Finegan <i>et al.</i> ⁵¹	133	117	Thalamic, caudate, and hippocampal atrophy and shape alterations, both in ALS and in PLS
Jin <i>et al.</i> ⁵²	108	90	Cortical thinning of the precentral gyrus with focus on the head-face region in bulbar-onset and on the upper-limb region in cervical-onset
Machts <i>et al.</i> ⁵³	31	29	Hippocampal volume reduction with shape deformities in the right hippocampal head and body region in vertex analysis
Welton <i>et al.</i> ⁵⁴	21	63	Trend toward atrophy of the precentral gyrus, as part of a composite score for disease classification
Senda <i>et al.</i> ⁵⁵	67	38	Gray matter atrophy in the precentral gyrus, basal ganglia, and frontotemporal lobes, more pronounced in rapid progression
Placek <i>et al.</i> ⁵⁶	109	113	Cortical thinning within the frontal and temporal lobes
Steinbach <i>et al.</i> ⁵⁷	85	62	Gray and white matter density decreases in the frontal and temporal lobes, as well as disease phase-related spread to frontal, temporal, and occipital gray matter areas

(Continued)

Table 1. (Continued)

Publication	ALS	Controls	Main finding
Chenji <i>et al.</i> ⁵⁸	53	43	Decreased gray matter density in the precentral gyrus, and premotor and medial prefrontal cortex, associated with verbal fluency
Christidi <i>et al.</i> ⁵⁹	50	40	Hippocampal atrophy, most pronounced in the cornu ammonis 2/3 subfield and the hippocampus-amygdala transition area
Omer <i>et al.</i> ⁶⁰	30	40	Gray matter atrophy in the pre- and postcentral gyri, or bitofrontal cortex, Broca area, and the frontal/temporal lobes in ALS-FTD
Finegan <i>et al.</i> ⁶¹	33	100	Gray matter atrophy and cortical thinning in the precentral gyrus and left pars opercularis region; cerebellar atrophy in PLS and cortical thinning in the postcentral gyrus in ALS
Finegan <i>et al.</i> ⁶²	39	100	Gray matter atrophy and cortical thinning in the precentral gyrus, more widespread in 'definite' versus 'probable' PLS
Tae <i>et al.</i> ⁶³	32	43	Regional shape contractions that suggest local atrophy in both pallida, the right putamen, and the right nucleus accumbens
Bede <i>et al.</i> ⁶⁴	133	100	Progressive, multisegmental brainstem atrophy with medullar predominance, both in ALS and in PLS
Cheng <i>et al.</i> ⁶⁵	60	60	Cortical thinning in right precentral gyrus, superior frontal gyrus, and superior temporal gyrus
Finegan <i>et al.</i> ⁶⁶	40	100	Widespread gray and white matter atrophy in PLS, most pronounced in the precentral gyrus, frontal lobe, thalamus, corpus callosum, and corticospinal tract
Ratti <i>et al.</i> ⁶⁷	22	115	Gray matter atrophy in the precentral gyrus, the dorsomedial and dorsolateral prefrontal cortex, and the orbitofrontal cortex, mainly driven by ALS-FTD
van der Burgh <i>et al.</i> ⁶⁸	268	156	Progressive cortical thinning in the precentral gyrus, frontal, and temporal regions; atrophy of the hippocampi, left amygdala, left accumbens nucleus, and right thalamus
Hensiek <i>et al.</i> ⁶⁹	206	104	Lower T1 intensity of the tongue in bulbar-onset compared with limb-onset ALS
Gorges <i>et al.</i> ⁷⁰	251	112	Atrophy of the hypothalamus is related to body mass index and unrelated to disease stage
Chen <i>et al.</i> ⁷¹	283	255	White matter atrophy in the precentral gyrus, supplementary motor areas, left middle cerebellar peduncle, and right cerebellum, involving several fibers and tracts
Machts <i>et al.</i> ⁷²	158	86	Cortical thinning in the right precentral gyrus; trend toward cortical thinning in the left precentral gyrus
ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; PLS, primary lateral sclerosis.			

Table 2. Summary of microstructural/diffusion properties findings from studies with DTI data in ALS.

Publication	ALS	Controls	Main finding
Illán-Gala <i>et al.</i> ²³	31	37	Increased cortical mean diffusivity in prefrontal regions in patients with cognitive or behavioral impairment
Baek <i>et al.</i> ⁷³	96	47	Altered diffusivity in the corticospinal tract at the brainstem and in the cerebellar peduncle area
Schuster <i>et al.</i> ²⁶	60	69	White matter degeneration of all segments of the corticospinal tract and the corpus callosum predicted survival via binary logistic regression
Bharti <i>et al.</i> ⁴⁴	71	56	Altered diffusivity in the superior, middle, and inferior cerebellar peduncle
Cheng <i>et al.</i> ²⁴	60	60	Reduced fiber density and fiber bundle cross-section in the corticospinal tract and the body of the corpus callosum
Qiu <i>et al.</i> ³⁹	60	60	Reduced FA in left corticospinal tract and the body of the corpus callosum
Christidi <i>et al.</i> ³⁴	56	25	Reduced FA in the corticospinal tract, the body and splenium of the corpus callosum, and major associative and limbic tracts
Rajagopalan <i>et al.</i> ⁷⁴	45	14	Loss of subcortical fibers and reduced FA in the corticospinal tract
Branco <i>et al.</i> ³²	50	38	Reduced FA in the fornix of ALS patients with behavioral impairment; no changes in the body of the corpus callosum
Tu <i>et al.</i> ⁴⁷	20	31	Increased diffusivity in thalamic parcellations associated with the left frontal lobe, bilateral premotor cortex, bilateral motor cortex, right somatosensory cortex, and bilateral parietal lobe
Weidman <i>et al.</i> ⁷⁵	43	15	Altered diffusivity in the corticospinal tract
Christidi <i>et al.</i> ³⁹	50	40	Altered diffusivity in the fornix and the right perforant pathway zone
Tu <i>et al.</i> ⁷⁶	39	25	Abnormal diffusivity in the rostral body, posterior midbody, and isthmus of the corpus callosum
Finegan <i>et al.</i> ⁵²	39	100	Altered diffusivity in the corticospinal tracts throughout their intracranial course and in the corpus callosum
Müller <i>et al.</i> ⁷⁷	46	23	FA reduction along the corticospinal, corticorubral, and corticopontine tracts in ALS and progressive bulbar palsy
Borsodi <i>et al.</i> ⁷⁸	27	35	Altered diffusivity in the corticospinal tract
Ferraro <i>et al.</i> ¹¹	123	78	Altered diffusivity in the corticospinal tract and in specific segments of the corpus callosum contribute to disease classification in a random forest analysis
Kassubek <i>et al.</i> ⁷⁹	67	31	Reduced FA in the corticospinal, corticopontine, and corticorubral tracts, the corticostriatal pathway, and the proximal portion of the perforant path
Müller <i>et al.</i> ⁸⁰	100	50	FA reduction in frontal and prefrontal brain areas, the corticospinal and corticopontine and corticorubral tracts, the corticostriatal pathway, and the proximal portion of the perforant path
Welton <i>et al.</i> ⁵⁴	21	63	Lower diffusion kurtosis measures in the motor cortex, as part of a composite score for disease classification
de Albuquerque <i>et al.</i> ²⁵	53	64	Widespread diffusivity abnormalities in the corticospinal tract and the corpus callosum, with longitudinal progression
Christidi <i>et al.</i> ⁸¹	50	25	Altered diffusivity in the corticospinal tract, the body and genu of corpus callosum, and in several extramotor white matter tracts, more pronounced in patients with cognitive impairment

(Continued)

Table 2. (Continued)

Publication	ALS	Controls	Main finding
Senda <i>et al.</i> ⁵⁵	67	38	Decreased FA in the corticospinal tract (corona radiata and internal capsule), the frontotemporal lobes, and the basal ganglia, more pronounced in rapid progression
Omer <i>et al.</i> ⁶⁰	30	40	Widespread diffusivity changes in the corticospinal tract, in frontal and temporal regions and in the brainstem in ALS-FTD patients; no findings in ALS without behavioral or cognitive deficits
Bede <i>et al.</i> ¹⁰	75	75	Altered diffusivity in the corticospinal tract and in the corpus callosum contributes to disease classification in a canonical discriminant analysis
Agosta <i>et al.</i> ³¹	67	22	Diffusivity changes involving the motor and extramotor pathways
Trojisi <i>et al.</i> ³⁷	54	22	Altered diffusivity in the body of corpus callosum and the superior part of corticospinal tract, both in slow and in fast progressors
Steinbach <i>et al.</i> ⁸²	145	69	Altered diffusivity in the corticospinal tract, body and genu of the corpus callosum, and adjacent corona radiata, as well as brainstem and cerebellar pathways
Chenji <i>et al.</i> ⁵⁸	53	43	Altered diffusivity in the corticospinal tract; in ALS with impaired verbal fluency or executive dysfunction: altered diffusivity in the corpus callosum, cingulum, and superior longitudinal fasciculus
Bao <i>et al.</i> ⁸³	33	32	Increased diffusivity in premotor, primary motor, primary, and secondary somatosensory areas, along the corticospinal tract, and in the body of the corpus callosum
Finegan <i>et al.</i> ⁶¹	33	100	Altered diffusivity in the corticospinal tract (centrum semiovale, corona radiata and internal capsule), body of the corpus callosum, splenium, brainstem, and cerebellum in PLS
Trojisi <i>et al.</i> ⁸⁴	36	35	Reduced FA in subcortical areas of the corticospinal tract and in the body of corpus callosum
Trojisi <i>et al.</i> ³⁸	32	21	Altered diffusivity in subcortical areas of the corticospinal tract, the body and genu of the corpus callosum, uncinate fasciculus, and the superior longitudinal fasciculus
Cheng <i>et al.</i> ⁶⁵	60	60	Decreased FA in the right corticospinal tract and the posterior body of the corpus callosum
Zhang <i>et al.</i> ⁸⁵	396	360	Reduced FA in the corticospinal tract, the corpus callosum, and the left superior longitudinal fasciculus
Gorges <i>et al.</i> ¹⁹	2064	1688	Microstructural alterations along the corticospinal tract, frontal and midbrain regions, the corticorubral and corticopontine tracts, the corticostriatal pathway, and in hippocampal regions
Müller <i>et al.</i> ⁸⁶	166	92	Widespread FA reduction along the corticospinal tract, corticopontine and corticorubral tracts, corticostriatal pathway, proximal portion of the perforant path, and in frontal and prefrontal brain areas
Müller <i>et al.</i> ⁸⁷	176	88	FA reduction in the upper and lower corticospinal tract, corticopontine and corticorubral tract, corticostriatal pathway, and the frontal and temporal lobes, both in ALS and in PLS
Kalra <i>et al.</i> ⁸⁸	66	43	Progressive FA reduction in corticospinal tract and in the frontal lobes; reduced FA in corticopontine and corticorubral tracts, the corticostriatal pathway, and the midbrain

ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; DTI, diffusion tensor imaging; FA, fractional anisotropy; PLS, primary lateral sclerosis.

Table 3. Summary of main functional and structural connectivity findings from studies with rs-fMRI data in ALS.

Publication	ALS	Controls	Main finding
Functional connectivity: resting-state functional magnetic resonance imaging			
Ogura <i>et al.</i> ³⁶	71	69	Decreased intrinsic connectivity in the posterior right fusiform and the lingual gyrus, related to semantic deficit in ALS
Trojisi <i>et al.</i> ³⁷	54	22	Decreased functional connectivity in the sensorimotor network, default mode network, frontoparietal network, and salience network
Ma <i>et al.</i> ⁸⁹	54	54	Increased dynamic regional homogeneity in the left lingual gyrus; decreased dynamic regional homogeneity in the left rectus gyrus and left parahippocampal gyrus
Li <i>et al.</i> ⁹⁰	38	35	Decreased short-range functional connectivity density in the primary motor cortex; increased long-range functional connectivity density in the premotor cortex
Loewe <i>et al.</i> ⁹¹	64	38	Decreased functional connectivity in motor-related areas; widespread functional connectivity changes across the temporo-occipital cortex
Hu <i>et al.</i> ²⁸	42	21	Decreased regional homogeneity in sensorimotor cortices; increased regional homogeneity in parietal and cerebellar areas, associated with cognitive impairment
Bharti <i>et al.</i> ⁴⁴	71	56	Decreased functional connectivity between the dentate nucleus and the right precentral gyrus/the supplementary motor area/frontal, parietal, temporal, and infratentorial regions
Qiu <i>et al.</i> ³⁹	60	60	Decreased functional connectivity between the precentral cortex and sensorimotor areas/parieto-occipital regions/the cerebellum
Trojisi <i>et al.</i> ³⁸	32	21	Decreased functional connectivity within the limbic system and between the limbic system and frontal/cerebellar areas
Agosta <i>et al.</i> ³¹	67	22	Increased functional connectivity within the sensorimotor network and the dorsal attention network
Cheng <i>et al.</i> ⁶⁵	60	60	Decreased self-inhibitory influence in the precentral gyrus
Chen <i>et al.</i> ⁹²	32	45	Decreased temporal variability in functional network connectivity, with aberrant connectivity between the default mode network/cognitive control network and the sensorimotor network
Basaia <i>et al.</i> ⁹³	173	79	Increased functional connectivity in sensorimotor, basal ganglia, and frontal areas and to a lesser extent in temporal and parietal areas

(Continued)

Table 3. (Continued)

Publication	ALS	Controls	Main finding
Structural connectivity and connectomics			
Meier <i>et al.</i> ⁹⁴	60	120	Connectome-based random walker aggregation levels can explain disease stages and contribute to survival prediction via deep learning
Serra <i>et al.</i> ⁹⁵	39	15	Strong-Weak Pruning for brain network identification reveals impaired structural connectivity between the frontal and temporal/parietal cortex and between the temporal and occipital cortex
van der Burgh <i>et al.</i> ⁶⁸	268	156	Reduced structural connectivity in the motor network
Basaia <i>et al.</i> ⁹³	173	79	Lower mean local efficiency as a global network property and regionally decreased structural connectivity in sensorimotor, basal ganglia, frontal, and parietal areas
Zhang <i>et al.</i> ⁹⁶	60	60	Increased path length, clustering coefficient, small-world index, and local efficiency; decreased global efficiency; altered nodal degree and betweenness in frontal lobe areas
Fortanier <i>et al.</i> ⁹⁷	25	26	Decreased global efficiency and decreased mean degree in the left postcentral gyrus and in the left interparietal and transverse parietal sulci
ALS, amyotrophic lateral sclerosis; rs-fMRI, resting-state functional magnetic resonance imaging.			

Table 4. Summary of main susceptibility findings from studies with SWI or T2*-weighted data in ALS.

Publication	ALS	Controls	Main finding
Acosta-Cabronero <i>et al.</i> ³⁵	28	39	Increased susceptibility in the motor cortex, premotor areas, substantia nigra, globus pallidus, and red nucleus
Lee <i>et al.</i> ⁹⁸	26	26	Increased susceptibility in the motor cortex and decreased susceptibility in subcortical regions
Weidman <i>et al.</i> ⁷⁵	43	15	Increased motor cortex susceptibility
Contarino <i>et al.</i> ⁴³	42	23	Significant susceptibility skewness and trend toward increased susceptibility in the prefrontal cortex
Conte <i>et al.</i> ⁹⁹	48	28	Increased motor cortex susceptibility
Conte <i>et al.</i> ¹⁰⁰	47	38	Increased susceptibility skewness in the precentral cortex, driven by upper motor neuron involvement
Borsodi <i>et al.</i> ⁷⁸	24	33	Increased susceptibility in the left corticospinal tract in bulbar ALS
Welton <i>et al.</i> ⁵⁴	21	63	Increased susceptibility/iron concentration in the motor cortex, as part of a composite score for disease classification
ALS, amyotrophic lateral sclerosis; SWI, susceptibility weighted imaging.			

Table 5. Summary of main findings from studies with special MRI modalities or analyses in ALS.

Publication	Method	ALS	Controls	Main finding
Reischauer <i>et al.</i> ¹⁰¹	MRS	24	27	Altered diffusivity for several spectroscopic parameters in the precentral gyrus; reduced tNAA in the precentral gyrus
Grapperon <i>et al.</i> ¹⁰²	Sodium-MRI	27	30	Higher total sodium concentration in the right precentral gyrus and the corticospinal tract
Ishaque <i>et al.</i> ¹⁰³	Texture analysis	83	74	Texture analysis revealed alterations in the precentral gyrus, corticospinal tract, insula, basal ganglia, hippocampus, and frontal regions, including subcortical white matter
Müller <i>et al.</i> ¹⁰⁴	Texture analysis	152	82	Increased entropy in area II of the corpus callosum; increased inhomogeneity in areas I–III of the corpus callosum
Elahi <i>et al.</i> ¹²	Texture analysis	69	42	Texture analysis of T1-slices of the corticospinal tract achieves disease classification in an ensemble stacking machine learning model
Wirth <i>et al.</i> ¹⁰⁵	T2-weighted FLAIR	28	31	Increased amount of FLAIR lesions in male patients, predominantly detected in the superior and posterior corona radiata, anterior capsula interna, and posterior thalamic radiation
Fabes <i>et al.</i> ¹⁰⁶	T2w FLAIR	33	21	Progressive FLAIR hyperintensity of the corticospinal tract
Shen <i>et al.</i> ²⁷	CBF	55	20	Reduced cerebral blood flow in the frontal lobe, insula, corpus callosum, and caudate in ALS-FTD
Welton <i>et al.</i> ⁵⁴	CBF	21	63	No significant difference in motor cortex perfusion
ALS, amyotrophic lateral sclerosis; CBF, cerebral blood flow; FLAIR, fluid-attenuated inversion recovery; FTD, frontotemporal dementia; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.				

Alterations in susceptibility-weighted imaging (SWI)

Twenty datasets were reviewed (Table 4). Increased susceptibility in the precentral gyrus was consistently reported.^{54,75,99} In addition, few studies reported increased susceptibility in sub-cortical structures and decreased susceptibility in the corticospinal tract.³⁵ Of note, the use of phase difference-enhanced (PADRE) MRI enabled to identify a characteristic low-signal intensity layer in the precentral cortex in 50% of ALS subjects, a finding which had been named the ‘zebra sign’ in an earlier publication due to the appearance of three- or four-layer organizations in the precentral cortex in ALS.^{111,112}

Alterations in other MRI parameters or analyses

Twenty-six datasets were reviewed (Table 5). In a multicenter study, texture feature extraction [Modified Co-occurrence Histograms of Oriented Gradients (M-CoHOG)] from the corticospinal tract was able to differentiate patients with ALS from healthy controls.¹² Texture analysis of the corpus callosum showed significant differences in homogeneity and entropy in the motor segment.¹⁰⁴ By use of magnetic resonance spectroscopy (MRS), reduced N-acetylaspartate and increased myo-inositol levels were reported in the precentral gyrus.¹⁰¹ In addition, sodium-MRS revealed higher total sodium concentration in the right precentral gyrus and the corticospinal tract.¹⁰² Longitudinal fluid-attenuated inversion recovery (FLAIR) imaging demonstrated progressive hyperintensity of the corticospinal tract.¹⁰⁶ Cerebral blood flow (CBF) imaging showed hypoperfusion in several brain regions,²⁷ however, not confirmed in a recent study.⁵⁴

Semi-quantitative analysis

For the semi-quantitative analysis, it was counted how many of the included studies reported a specific area as a significant finding (note that this approach may have biased the analysis by under-reporting or overreporting of specific results). The findings from the semi-quantitative analysis are summarized in Table 6. In morphometry studies, the precentral gyrus, the thalamus, the hippocampus, the amygdala, the insula, the anterior cingulate cortex (ACC), the orbitofrontal cortex, and the middle and inferior frontal gyri

were most commonly reported. In DTI studies, the corticospinal tract, corticopontine/corticorubral tract, corticostriatal pathway, proximal portion of the perforant pathway, and the corpus callosum were most commonly reported. SWI and MRS studies showed abnormalities mostly in the motor cortex. In rs-fMRI studies, abnormalities were most commonly reported in the pre- and postcentral gyri, frontal and temporal lobe, the operculum, the insula and the lingual gyrus. In connectome studies, decreased global efficiency was the only consistent result.

Discussion

Summary

This systematic review provides a comprehensive overview of neuroimaging findings in ALS that can be used as features for disease classification in an ML model. In accordance with a previous systematic review and neuropathological findings,^{16,107,113,114} neuroimaging biomarkers were most commonly reported in the motor cortex and the corticospinal tract, together with frontal and temporal areas in later stages. Regarding feature selection, we provide a list of our findings in Table 6.

Brain structures in neuroimaging in ALS

The corticospinal tract, the corticopontine/corticorubral tract, the corticostriatal pathway, and the perforant pathway were among the most frequently reported regions that exhibited diffusivity changes. These tracts have previously been described as stage-dependent,^{3,79} which can be helpful in ML models when the presence of late-stage findings raises the confidence of the prediction.

The combination of structural and functional neuroimaging parameters in one ML model is very intriguing because it is expected that the complementary nature of these biomarkers as well as the low correlation between them theoretically might improve classification accuracy. Indeed, our review identified several candidate regions that could be included as features in such an ML model. However, both increased and decreased functional connectivity were reported with no clear directional effect. It can be argued that this inconsistency could ultimately introduce

Table 6. Comprehensive list of candidate regions for each modality to be included as feature in ML models for disease classification from cranial MRI in ALS.

Modality	Main regions	Further regions
T1	Precentral gyrus, thalamus, hippocampus, amygdala, insula, ACC, orbitofrontal cortex, middle frontal gyrus, inferior frontal gyrus	Paracentral lobule, operculum, temporal pole, postcentral gyrus, posterior cingulate, superior temporal gyrus, medial frontal cortex, parahippocampal gyrus, caudate, putamen, nucleus accumbens
DTI	Corticospinal tract (subcortical, superior corona radiata, posterior limb of the internal capsule, cerebral peduncle, brainstem), corticopontine/corticorubral tract, corticostriatal pathway, perforant pathway, corpus callosum (genu, body and splenium)	Frontal and temporal lobe (as a whole), corona radiata, superior longitudinal fascicle
rs-fMRI	Precentral gyrus, postcentral gyrus, superior and middle frontal gyrus, middle temporal gyrus, operculum, insula, lingual gyrus	Inferior frontal gyrus, superior parietal lobule, supramarginal gyrus, angular gyrus, precuneus, occipital fusiform gyrus, occipital pole
SWI	Precentral gyrus	Striatum (higher susceptibility) and corticospinal tract (lower susceptibility)
MRS	Precentral gyrus (NAA and myo-inositol)	Supplementary motor area, postcentral gyrus, brainstem/pontine region
connectomics	Global efficiency	Nodal degree in frontal lobe
ACC, anterior cingulate cortex; ALS, amyotrophic lateral sclerosis; DTI, diffusion tensor imaging; ML, machine learning; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, n-acetylaspartate; SWI, susceptibility-weighted imaging.		

more noise than signal, especially when the theoretical background of this inconsistency remains ill-defined. In contrast, it may be of advantage to approach rs-fMRI feature extraction based on neuropathological concepts.¹¹⁵ To incorporate functional connectivity measures as features in an ML model, a higher level of data preprocessing might be needed. Without preselection, the main challenge in analyzing rs-fMRI is the high amount of features that would have to be incorporated into the model. Early attempts have used spatial templates and principal component analysis for dimensionality reduction with some success.^{7,8} At any rate, implementing rs-fMRI data into ML models remains a challenge, and for such a combination of functional and structural data, multiple combined ML models may be needed.

In addition to the most commonly reported neuroimaging biomarkers in ALS, our analysis

identified further promising candidates. T1w MRI of the tongue revealed decreased signal intensity in patients with ALS.⁶⁹ Extracting these data might be a makeshift method of measuring lower motor neuron (LMN) degeneration. With respect to ML, measuring LMN degeneration could increase classification accuracy, as little correlation with other [upper motor neuron (UMN)] features is expected. Another biomarker that caught our attention was the atrophy of the hypothalamus. Unlike other biomarkers, hypothalamic atrophy did not relate to disease stage and was detectable very early on, even in pre-symptomatic cases⁷⁰; this association has been investigated in orbitofrontal-hypothalamic projections in a murine ALS model and in human patients.¹¹⁶

One of the more recent techniques in ML is texture analysis. While even general image

recognition models like ResNet and VCG-16 are capable of detecting a distinct signature in the corticospinal tracts of patients with ALS, custom-tailored solutions are by far more powerful.^{13,14} Using M-CoHOG in an elaborated ML model, Elahi *et al.* achieved classification with up to 80% accuracy.¹² Müller *et al.* were able to differentiate patients with PLS and healthy controls with a sensitivity of 73% and a specificity of 84% using a single texture parameter (homogeneity) in the corpus callosum.¹⁰⁴ These types of analyses support the strength of ML and could substantially boost the accuracy of ML models.

SWI and MRS were found to only show abnormalities in the motor cortex. While this information *per se* can be very useful, there are other MRI modalities that can assess the integrity of the motor cortex without expanding the MR measuring time. Although it can be argued that having more features is preferable, redundancy might not increase diagnostic accuracy, but lower it due to worse SFR. With this in mind, adding these sequences to a standard protocol is hard to justify for ML classification. There were several MRI modalities with scarce data, like arterial spin labeling (ASL) for cerebral blood flow quantification. The contribution of these modalities to multiparametric classification models has to await a higher number of studies in the future. It has been concluded that the most important MRI sequences in this regard are T1w, DTI, and rs-fMRI, with MRS only being optional.^{117,118} Given that ML models usually need large datasets, multicenter initiatives are important for improving the methodological quality of future studies.

Limitations

This systematic review was confined to cranial MRI. However, there are plenty of studies that investigated spinal pathologies that can be considered to serve as biomarkers in ALS, for example, spinal diameter.¹¹⁹ We decided against the inclusion of these studies in this review for two reasons. First, adding spinal MRI to an ML model would require a time-consuming MRI protocol that may not be suited for routine applications. Second, spinal MRI in ALS mostly measures pathologies of the corticospinal tract which can also be measured in the brain. Features extracted from spinal MRI might thus be redundant. Most of the studies compared patients with ALS with healthy controls. It can be argued that this is not useful in a diagnostic

setting, where ALS has to be differentiated from its mimic disorders. However, many mimic disorders of ALS are peripheral neuropathies which are expected to be associated with a normal cranial MRI. When comparing patients with ALS with healthy controls and mimic disorders, Ferraro *et al.* found that the model actually performed better with the latter.¹¹ Although more studies with mimic disorders are needed, building an ML model with healthy control subjects (and fine-tuning it with mimic disorders) might suffice. In this review, we did not differentiate our findings between the clinical phenotypes of the ALS spectrum disorders (including the proportion of UMN/LMN involvement), that is, 'classic' ALS and primary lateral sclerosis, UMN-predominant (pyramidal), LMN-predominant (including flail arm and flail leg syndrome), and pure LMND (progressive muscular atrophy). Future studies should address fine phenotypic characterization given that there is a need for models discriminating not only classic ALS from mimic conditions but also classic ALS from pure/predominant UMN and pure/predominant LMN disease forms. Finally, our review focused on the neuroimaging domain, which means that the clinical domain, that is, a detailed assessment of the application of the ALS diagnostic criteria and their accuracy, was beyond the scope of this study. We used the inclusion criterion that the subjects with ALS had been diagnosed according to common diagnostic guidelines without further specification, while neuropathological confirmation was not a criterion due to the general lack of autopsies.

Conclusion

This review summarizes the most important findings that could be used as features in an ML model (Table 6). DTI and volumetric data can be considered to be the most robust features. Integrating functional or structural connectivity data might be challenging and may require dimensionality reduction techniques. Recently, texture analyses have demonstrated convincing results that may advance the field toward classification with higher accuracy. In the future, ML and multiparametric neuroimaging data might provide physicians with a powerful diagnostic tool.

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Author contributions

TDK was involved in study concept and design, data analysis and interpretation of data, and drafting of manuscript. H-PM was involved in interpretation of data and critical revision of manuscript for intellectual content. ACL was involved in interpretation of data and critical revision of manuscript for intellectual content. JK was involved in study concept and design, interpretation of data, study supervision, and critical revision of manuscript for intellectual content.

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