The Present and the Future of Neuroimaging in Amyotrophic Lateral Sclerosis

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ALS, also known as motor neuron disease, is a neurodegenerative disorder characterized by a progressive muscular paralysis reflecting degeneration of motor neurons in the primary motor cortex, brain stem, and spinal cord. The phenotypic expression of ALS is highly heterogeneous and determined by 4 elements: 1) body region of onset, 2) relative mix of UMN and LMN involvement, 3) rate of progression, and 4) cognitive impairment. In approximately 5%–10% of patients, the disease is inherited; 20% of these individuals have a mutation of the \( SOD1 \) gene; approximately 2%–5% of the \( TARDBP \) (\( TDP-43 \)) gene; and 2%–4%, of the \( FUS/TLS \) gene. Most patients with ALS, however, have no obvious family history and have sporadic ALS. To date, the only specific marker of sporadic ALS is the presence of inclusions staining positively for ubiquitin and \( TDP-43 \) in degenerating motor neurons.

Despite technical advances in medicine in the last century, the diagnosis of sporadic ALS relies on the interpretation of clinical symptoms and signs (ie, signs suggestive of combined UMN and LMN degeneration, together with disease progression compatible with a neurodegenerative disorder). Paraclinical and laboratory tests are used only to exclude “ALS-mimic” syndromes. In ALS, the absence of a disease marker for UMN and LMN involvement has 2 main negative consequences. First, the delay from onset of the disease to diagnosis of ALS can vary between 13 and 18 months; and the diagnostic delay may even be greater in patients who present with isolated LMN signs. Such a delay precludes early initiation of neuroprotective treatments. Second, the phenotypic heterogeneity of the disease is an important confounding factor in clinical trials because it results in a limited inclusion of patients (which requires the fulfillment of the revised El Escorial criteria) and in a highly variable treatment response.

Several neuroimaging modalities have been used with varying success either to aid the clinical process of establishing a diagnosis of sporadic ALS or to monitor disease progression. Conventional MR imaging of the brain and spinal cord has an important role in the differential diagnosis. \( H-\text{MR spectroscopy and DTI} \) hold promise for detecting and quantifying subclinical UMN damage. The use of fMRI has provided evidence for cortical reorganization in patients with ALS and has contributed to achieving a more complete picture of the ALS-related extramotor involvement. This review summarizes the main results obtained from the application of conventional and nonconventional MR imaging in patients with ALS and highlights many areas for which more research is warranted.

**Conventional MR Imaging Findings**

Routine anatomic imaging of the brain and/or the spinal cord is helpful in ruling out diseases that mimic ALS with varying degrees of UMN and LMN signs. The revised criteria of the World Federation of Neurology Research Group on Motor Neuron Diseases state that conventional MR imaging studies are not required in those cases that have a clinically definite disease with a bulbar or a pseudobulbar onset. On the other hand, in patients with clinically probable or possible ALS, MR imaging can be useful in excluding several...
ALS-mimic syndromes, including cerebral lesions (eg, multiple sclerosis and cerebrovascular disease), skull base lesions, cervical spondylotic myelopathy, other myelopathy (eg, foramen magnum lesions, intrinsic and extrinsic tumors, and syringomyelia), conus lesions, and thoracolumbar sacral radiculopathy.12

In patients with ALS, signal-intensity changes on conventional MR imaging (ie, T2-weighted, PD-weighted, and FLAIR sequences) can be observed along the CST.14-23 Typically, CST changes, which are best followed on coronal scans, appear as areas of bilateral increased signal intensity from the centrum semiovale to the brain stem. However, the frequency of CST hyperintensities in patients with ALS varies significantly in the different studies (ranging from 15% to 76%), and it is not clear yet which may be the most sensitive MR image to detect them (Fig 1A-D). The combined application of T2-weighted, PD-weighted, and FLAIR images has recently reached a sensitivity of approximately 62%.24 In addition, CST signal-intensity changes do not correlate with clinical scores.17 More remarkably, CST hyperintensities have also been described in healthy subjects,20 and in patients with other conditions, such as Krabbe disease,25 X-linked Charcot-Marie Tooth neuropathies,26 and adrenomyeloneuropathy.27

In patients with ALS, a characteristic low signal intensity (hypointense rim) of the precentral cortex on T2-weighted images can be observed (Fig 1E).16,18,19,21,22,28 However, such a change is neither sensitive nor specific to the pathology of ALS. Symmetric T2 signal-intensity changes in the anterior temporal subcortical WM have been described in patients with ALS and dementia (Fig 1F).29,30 Pathologically, such hyperintensities correspond to loss of myelin,30 WM degeneration,29 and gliosis.29

Significant lower whole brain volume has been found in patients with ALS relative to healthy controls.31-33 Global brain atrophy is, however, relatively mild.

Consistent with pathologic data, T2 and T1 hyperintensities of the anterolateral columns of the cervical cord have been observed in patients with ALS.21,22,34 Such hyperintensities are likely to have higher specificity than signal-intensity changes on brain MR images.21,34 T1 hyperintensity of the anterolateral cervical cord has been associated with a younger age and a rapid disease progression.22

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Fig 1. Conventional MR imaging findings in patients with ALS. A—D, Hyperintensity at the subcortical precentral gyrus (A and B) and the centrum semiovale (C and D) on FLAIR (arrows, A and C) and T2-weighted (arrows, B and D) images of a 66-year-old patient with ALS. Modified with permission from Hecht et al.17 E and F, T2-weighted images obtained from a 58-year-old patient with ALS with dementia show hypointensity along the precentral cortices (arrowheads, E) and symmetric hyperintensity in the anterior temporal subcortical WM (arrows, F). A and D reprinted with permission from the Journal of the Neurological Sciences (2001;186:37–44). Copyright 2001, Elsevier Ltd.
Nonconventional MR Imaging Assessment of the Motor System

Regional Atrophy

Despite the consistent finding of cortical motor involvement in pathologic studies of ALS, in vivo MR imaging studies did not reach firm conclusions regarding the presence of motor/premotor cortical atrophy because this was reported by some authors (Fig 2), but not by others.

Using VBM to assess the regional distribution of WM loss, researchers have found atrophy of the CST in patients with ALS, which was more severe in patients with a bulbar onset. Patients with ALS showed atrophy of the cervical cord relative to controls, which significantly worsened during a 9-month follow-up.

$^1$H-MR Spectroscopy

In patients with ALS, $^1$H-MR spectroscopy studies demonstrated a decrease in NAA concentrations and ratios of NAA over Cr, Cho, and Cr + Cho in the motor cortex. The physiologic role of NAA in the central nervous system remains unclear. However, because NAA appears to be present only in neurons of the adult human brain and in their processes, the content of NAA is used as a biochemical marker of neuronal integrity. These findings have been recently confirmed at 3T. However, the diagnostic value of $^1$H-MR spectroscopy is poor because of the considerable overlap of the metrics of patients with those of healthy controls.

Patients with ALS showed decreased NAA/Cr and NAA/Cho ratios along the CST. Although the regional analysis of these data showed more pronounced $^1$H-MR spectroscopy changes in the precentral gyrus and corona radiata, NAA reduction in the brain stem has also been reported.

Cross-sectional studies have shown a moderate correlation between NAA concentration (and its ratios) in the motor cortex and clinical manifestations of ALS (ie, disease severity, extent of UMN signs, and maximum finger tapping rate). Patients with bulbar onset have the most severe pattern of motor cortex $^1$H-MR spectroscopy changes compared with those with a limb onset.

In addition to neuronal damage, increased glial cell activity, reflected by raised levels of mIns, has been demonstrated in the motor cortex of patients with ALS. Increased mIns levels are associated with motor cortex hypointensity on T2-weighted images. In a 3T $^1$H-MR spectroscopy study of patients with ALS, the NAA/mIns ratio provided better sensitivity and specificity for detecting disease than the individual metabolites and was the strongest correlation with disease severity.

DTI

Using either region of interest–based approaches or tractography, DTI studies of patients with ALS reported consistently decreased FA and increased MD values along the CST (Fig 3). Loss of pyramidal motor neurons in the primary motor cortex and axonal degeneration of the CST, together with the proliferation of glial cells, extracellular matrix expansion, and intraneuron abnormalities, may contribute to the observed CST DTI changes. The most pronounced decreased FA and increased MD have been shown in the posterior limb of the internal capsule.

Decreased FA in patients with ALS was found to correlate with disease severity, rate of disease progression, and clinical and electrophysiologic measures of UMN involvement. Patients with a bulbar onset exhibited the most marked FA decrease. In 2 studies, increased MD of the CST has been associated with disease duration.

Compared with controls, patients with ALS had significantly lower FA of the cervical cord, which was strongly associated with the ALSFRS scores (Fig 4). This finding indicates...
the presence of distortion of cord tissue geometry in ALS and
agrees with pathologic data showing a pronounced cord de-
generation and a reduction of the number of LMNs in the
anterior horns of the cord GM in patients with ALS.77

**MT Imaging**

Using T1-weighted MT images, 1 study showed hyperinten-
sities along the CST (consistent with CST degeneration) in 80% of
patients with ALS.78 T1-weighted MT imaging provided
better sensitivity and specificity for detecting disease than FLAIR images.78

Two MT imaging studies showed a reduction of the MTR in the CST from 2.6%79 to 20%80 in patients with ALS compared with controls. This finding was not confirmed by a recent study.24 MT contrast is the result of cross relaxation and chemical exchange between spins in the 2 pools of water protons: bound immobile protons associated with macromolecules (such as myelin) and free mobile protons associated with free water. MTR is a quantitative measurement of this phenomenon, and it is correlated to the amount of bound protons in the macromolecular matrix. Reduced MTR values have been associated with axonal degeneration and myelin breakdown.81 A possible explanation for the negative results in the study by Charil et al24 could be that gliosis secondary to axonal loss might have led to a pseudonormalization of the MTR.

fMRI

During motor tasks, fMRI demonstrated an increased activation of the contralateral sensorimotor cortex and the supplementary motor area (Fig 5A).82-85 Increased sensorimotor activation was also reported in the hemisphere ipsilateral to the movement.84 A spatial shift of recruitment to more anterior regions of the premotor cortex during upper limb movement was also observed in patients with ALS.85 In patients with ALS, increased activation of the inferior parietal cortex during a motor task has been reported. A relationship with task difficulty85 or a compensatory role of these motor-related areas82,85 has been suggested.

In ALS, motor execution was also associated with increased activations of areas involved in motor learning, such as the basal ganglia and the cerebellum (Fig 5A).83,86 It is suggested that an increase in movement-associated cortical activations beyond the primary motor cortex is associated with the degree of UMN involvement.86

Nonconventional MR Imaging Assessment of the Extramotor Regions

Regional Atrophy

The pattern of regional GM loss in patients with ALS extends beyond the motor cortex to the frontotemporal and parietal regions (Fig 2).31,32,36-38,40,41,44 The most severe atrophy of the frontal regions has been observed in patients with ALS and FTD.38 In addition, patients with ALS with even subtle cognitive and/or behavioral impairment (not meeting the criteria for a diagnosis of FTD77) demonstrated GM loss in the frontal, parietal, and limbic regions compared with those with no evidence of cognitive deficits.86 These findings are consistent with pathologic studies demonstrating ubiquitin-positive intraneuronal inclusions and neuronal loss extending beyond the motor system in patients with ALS with or without cognitive impairment.35

VBM studies in patients with ALS have provided evidence for WM atrophy in extramotor areas, which include the corpus callosum, the cerebellum, and the frontotemporal and occipital areas.31,33,45 In 1 study of cognitively impaired non-
demented patients with ALS, a more severe frontotemporal WM loss was associated with deficits on verbal fluency.\textsuperscript{45}

Significant longitudinal cortical atrophy during a period of \textless 1 year has been described in motor and prefrontal areas in patients both with\textsuperscript{89} or without (Fig 6)\textsuperscript{90} clinical symptoms typical of FTD.

\textit{\textsuperscript{1}H-MR Spectroscopy}

In patients with ALS, a decrease of NAA levels is not restricted to the motor cortex and CST but also occurs in premotor regions, the primary sensory cortex, and extramotor frontal regions, with relative sparing of the parietal lobe.\textsuperscript{53,63} A correlation was found between the decrease in the NAA/Cr ratio in the frontal lobe and deficits of executive functions.\textsuperscript{63}

\textit{DTI}

In patients with ALS, FA decrease has been found in the corpus callosum\textsuperscript{36,75,91-93} and in several WM regions in the frontal\textsuperscript{75,91,93} and temporal lobes.\textsuperscript{75,93} The topographic pattern of MD changes in patients with ALS has been investigated by a few studies, which showed increased MD in the corpus callosum and in frontal and temporal WM regions compared with controls.\textsuperscript{36,93}

\textit{fMRI}

Significantly reduced activation of the middle and inferior frontal gyri, anterior cingulate cortex, and parietal and temporal lobes was found in nondemented patients with ALS relative to controls during a letter fluency fMRI task (Fig 5B).\textsuperscript{94} A confrontation naming fMRI task also revealed an impaired activation of a prefrontal region (including Broca area) and areas of the temporal, parietal, and occipital lobes (Fig 5C).\textsuperscript{94}

This pattern of dysfunction correlated with cognitive deficits on both word fluency and confrontation naming.\textsuperscript{94}

Functional cortical changes have been observed in patients with ALS without cognitive/behavioral impairment during processing of socioemotional stimuli (ie, pictures of persons in emotional situations).\textsuperscript{95} Compared with controls, patients with ALS showed an increased activation of the right supramarginal gyrus.\textsuperscript{95}

The Near Future of Neuroimaging of ALS

The Prognostic Value of MR Imaging

In ALS, death due to respiratory failure follows on average 3–5 years after onset. However, the survival of individual patients with ALS is highly variable. A rapidly progressive course can occur, but approximately 10% of patients survive for a decade or more.\textsuperscript{96} Identifying predictors of progression and survival in ALS is important for both management of patients in clinical practice and design of new clinical trials. Older age at onset, bulbar site of onset, and a shorter time from symptom onset to diagnosis are the most consistently reported clinical predictors of shorter survival. A further contribution may come from MR imaging by the identification of disease changes earlier in the course of the disease. In one \textsuperscript{1}H-MR spectroscopy study, a reduced short-term survival has been associated with a lower NAA/Cho ratio.\textsuperscript{97}

MR Imaging to Monitor Disease Evolution

Longitudinal neuroimaging studies are likely to contribute to the monitoring of ALS progression. To date, only a few studies
have attempted to assess quantitatively the dynamics of non-
conventional brain structural changes in patients with ALS,
and they provided conflicting results. Some studies have dem-
onstrated a significant decrease of the NAA level in the motor
cortex, or the FA in the brain WM and cervical cord during <1 year. Changes of metabolite ratios and diffusivity
abnormalities were significantly correlated with progression
of disease severity. A serial \(^{1}H\)-MR spectroscopy study indi-
cated that a significant decrease of the NAA level also occurs
in brain extramotor regions after 9 months. However, in 1
prospective study of 30 patients with ALS, no significant
\(^{1}H\)-MR spectroscopy and DTI changes were observed. Similar
negative findings have been found by others.

The main limitation of longitudinal MR imaging studies
in ALS is the small sample sizes used. In addition, patients
recruited are typically advanced in their disease course,
which may imply that structural changes due to ALS pa-
thology had already occurred and stabilized at the time of
MR imaging, with only small changes occurring thereafter.
Finally, longitudinal MR imaging follow-up of patients
with ALS is limited by the declining ability of the patients to
tolerate the relatively long scanning time needed to obtain
meaningful quantitative MR imaging data. Future investi-
gations should involve larger groups of subjects, possibly
early in the course of the disease.

Despite many clinical trials and various advances in the
understanding of ALS, there has been little success in the
search for disease-modifying or neuroprotective agents. At
present, riluzole is the only approved drug that has been
shown to have a modest effect on prolonging life expectancy
in patients with ALS. The assessment of treatment effects on
\(^{1}H\)-MR spectroscopy measures in ALS is only preliminary. A
rapid increase of the NAA/Cr ratio in the motor cortex in
patients with ALS after only 1 day of riluzole treatment has
been reported. Conversely, no effect on cortical meta-
bolic function has been observed with gabapentin treat-
ment or brain-derived neurotrophic factor. The reliabil-
ity and reproducibility of measures of brain \(^{1}H\)-MR
spectroscopy also warrant further investigation. In addition,
the sensitivity and clinical relevance of \(^{1}H\)-MR spectroscopy
scans in detecting longitudinal ALS-related changes need to be
established before this technique is used for monitoring treat-
ment efficacy in the context of multicenter clinical trials.

Iron-Dependent MR Imaging
Iron deposition is known to accumulate in the brain with nor-
mal aging, and recent studies have shown that iron is also
involved in brain damage in many chronic neurologic disor-
ders, such as Alzheimer disease, Parkinson disease, and mul-
tiple sclerosis. An abnormal iron deposition has been sup-
posed to be the substrate of T2 hypointense areas seen in the
cortex of patients with ALS, T2* and other sequences used at \(3T\), such as T2*, T2', or T2-rho relaxometry;
magnetic field correlation imaging and susceptibility-
weighted imaging are likely to improve our ability to detect
iron deposition. As a consequence, iron-dependent MR imag-
ing may soon provide markers to monitor the progression
of brain damage in many neurologic diseases, including ALS.

fMRI
The difficulty of controlling task performance in patients with
ALS may be responsible for the variability of the results of
fMRI studies. The development of fMRI paradigms unbiased
by differences in task performance between patients with ALS
and controls, making the assessment of more disabled patients
feasible, should be considered. Motor imagery is known to
involve similar neural networks such as motor execution,
without being affected by confounding factors of effort and
strain. During a motor imagery task, patients with ALS
showed increased activation of the premotor and the primary
motor cortex. After 6 months, these differences persisted
with additional activations of the precentral gyrus and fronto-
parietal regions. In ALS, the resting-state fMRI studies
demonstrated not only changes in the premotor cortex but
also a reduced activation of the default mode network. Another
aspect that should be considered is the combination of
measures of functional connectivity with those of structural
damage of specific WM tracts, which is likely to improve our
understanding of the relationship between morphologic and
functional abnormalities observed in this condition.

Conclusions
Findings compatible with ALS on conventional MR imaging
are not consistently found and are nonspecific. By demon-
strating evidence of occult UMN degeneration in vivo, \(^{1}H\)-MR
spectroscopy and DTI may provide a faster and more defini-
tive diagnosis in suspected cases, leading to an earlier treat-
ment and enrollment in clinical trials. The extensive applica-
tion of modern MR imaging-based techniques to the study of
ALS has undoubtedly improved our understanding of disease
pathophysiology and may have a role in the identification of
potential biomarkers of disease progression. fMRI investiga-
tions of the motor and cognitive networks in patients with ALS have
demonstrated an altered recruitment of regions normally de-
voted to the performance of a given task and/or the recruit-
ment of additional areas in comparison with healthy subjects.

Nevertheless, there are many remaining challenges. New
techniques need to be harnessed and integrated into clinical
research and practice. New acquisition schemes and analysis
procedures require standardization and optimization so that
they can be used in multiple settings, both in natural history
studies and treatment trials. From the data available, it is evi-
dent that combining different MR imaging modalities that
are sensitive to different aspects of ALS pathology (eg, motor
and extramotor) is a promising way to further increase our
understanding of the mechanisms accounting for the accumu-
lation of irreversible disability in this condition. Moreover,
the emerging scenario from genetic studies indicates a consistent
overlap between the pathogenetic changes in most forms of
sporadic and familial ALS, thus suggesting that the appli-
cation of neuroimaging in familial patients with ALS may
allow identification of abnormalities that can hopefully be
translated to the assessment of sporadic ALS.

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