Basic Principles of Neuroimaging in Neuromuscular Diseases focusing on Amyotrophic Lateral Sclerosis

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NBML

Neuron → Network → Whole brain

Brain imaging: whole brain

Magnetic Resonance Imaging (MRI)

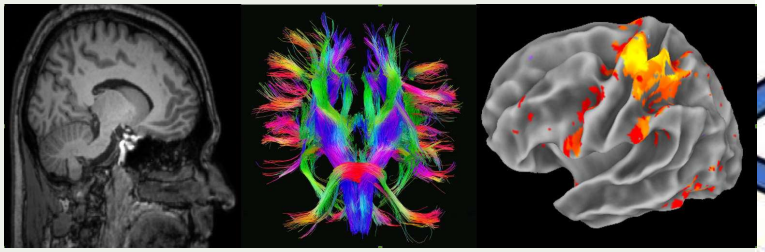
- Structural MRI
- Functional MRI
- Functional connectivity MRI

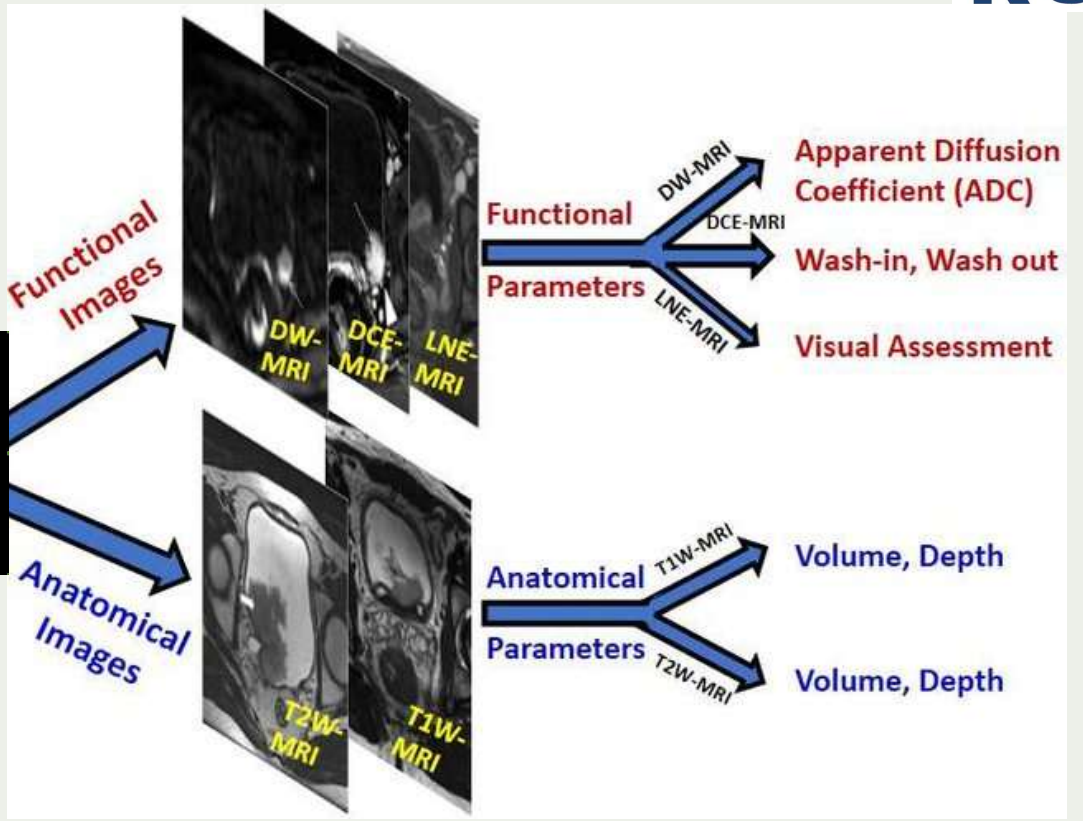
Computed tomography (CT)

Positron emission tomography (PET)

Advanced Techniques: EEG, MEG, MRS, SPECT, and DTI,…

Anatomical vs Functional?




Functional Images
DW-MRI
DCE-MRI
LNE-MRI
Functional Parameters
DW-MRI
DCE-MRI
LNE-MRI
Apparent Diffusion Coefficient (ADC)
Wash-in, Wash out
Visual Assessment
Anatomical Images
T2W-MRI
T1W-MRI
Anatomical Parameters
T1W-MRI
T2W-MRI
Volume, Depth
Volume, Depth

Overview of Motor Neuron Disorders

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By Sadegh Ghaderi/ PhD Candidate of Neuroimaging

This group of degenerative disorders is characterized clinically by weakness and variable wasting of affected muscles, without accompanying sensory changes.

Motor neuron disease in adults generally commences between 30 and 60 years of age.

There is degeneration of the anterior horn cells in the spinal cord, the motor nuclei of the lower cranial nerves, and the corticospinal and corticobulbar pathways.

The disorder is usually sporadic, but familial cases may occur and several genetic mutations or loci have been identified.

Cigarette smoking may be one risk factor.

Five varieties have been distinguished on clinical grounds:

Progressive Bulbar Palsy

Pseudobulbar Palsy

Progressive Spinal Muscular Atrophy

Primary Lateral Sclerosis

Amyotrophic Lateral Sclerosis

The terms motor neuron disease (MND) and amyotrophic lateral sclerosis (ALS) are often used synonymously.

Some basic neuroanatomy will help clarify the terms upper motor neuron (UNM) and lower motor neuron (LMN) and so will facilitate a more sophisticated understanding of MNDs as a family of related disorders, ranging from pure UMN to pure LMN to mixed UMN/LMN syndromes.

The role of imaging in the diagnosis of MNDs has traditionally been limited to excluding alternative diagnoses.

However, significant advances have been made in the last few years in the development of techniques to detect early signs of UMN involvement.

Upper Motor Neuron Disorder

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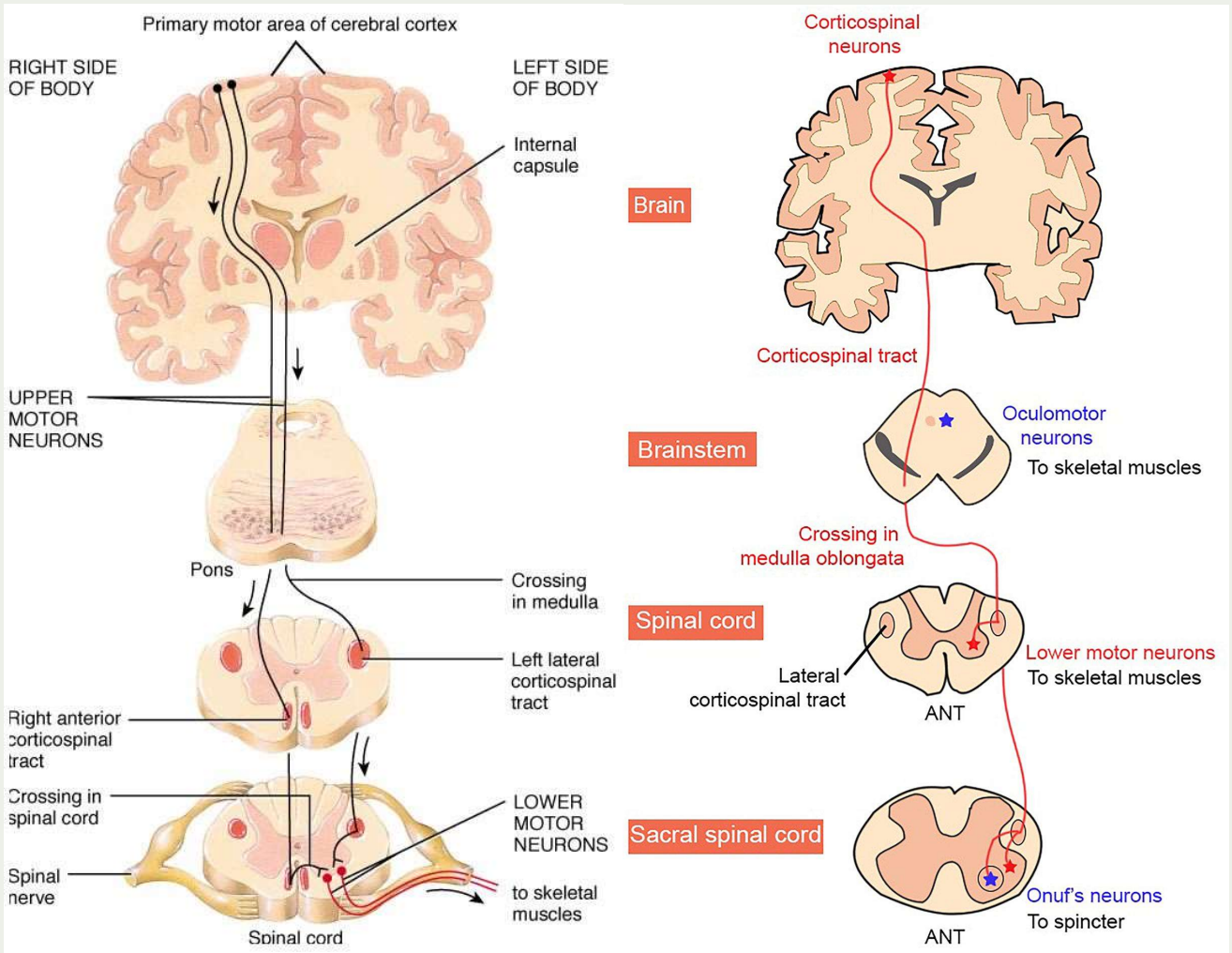
Upper motor neurons are neurons that have cell bodies in the primary motor cortex (Brodmann area 4) and the premotor area (Brodmann area 6) of the brain; they give rise to descending corticobulbar and corticospinal tracts that terminate on interneurons or motor neurons in cranial nerve motor nuclei or in spinal cord gray matter.

UMN disorders are characterized by poor motor control, with loss of dexterity, spasticity, and pseudobulbar (spastic bulbar) palsy.

Loss of muscle strength is generally mild until the disease is advanced because the LMNs are spared.


Primary motor area of cerebral cortex
RIGHT SIDE OF BODY
LEFT SIDE OF BODY
Internal capsule
UPPER MOTOR NEURONS
Pons
Crossing in medulla
Left lateral corticospinal tract
Right anterior corticospinal tract
Crossing in spinal cord
LOWER MOTOR NEURONS
Spinal nerve
to skeletal muscles
Spinal cord
Corticospinal neurons
Brain
Corticospinal tract
Brainstem
Oculomotor neurons
To skeletal muscles
Crossing in medulla oblongata
Spinal cord
Lower motor neurons
To skeletal muscles
Lateral corticospinal tract
ANT
Sacral spinal cord
Onuf's neurons
To spincter
ANT

Lower Motor Neuron Disorder

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Lower motor neurons are somatic efferent neurons whose cell bodies are located either in cranial nerve motor nuclei or in the ventral spinal cord. These are the final pathways between the central nervous system and the skeletal muscles.

Muscle weakness, atrophy, fasciculations, and cramps are the primary clinical symptoms in LMN diseases and are the result of muscle denervation.

Disorders of Both Upper and Lower Motor Neurons

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ALS is known by several others names, including Charcot disease (primarily in France), motor neuron disease, and (mostly in the United States) as Lou Gehrig's disease after the famous baseball player who developed the disease in the 1930s.

Amyotrophic Lateral Sclerosis;

Jean-Marie Charcot first described ALS in 1869

Fatal neurodegenerative disorder affecting both the upper and lower motor neurons

Affecting cerebral cortex, brainstem, and spinal cord

Inexorably progressive, resulting in death from respiratory failure

More than 90% of the cases are sporadic

Only about 5% or 10% are familial, most commonly autosomal dominant

Amyotrophic Lateral Sclerosis;

The prevalence of ALS is 5 to 10:100,000 population per year, with an approximately 3:1 male predominance

Paraneoplastic, occurring most commonly in patients with bronchial, prostate, or breast cancer and in lymphoproliferative diseases

Usual age at onset is 40 to 60 years

Amyotrophic Lateral Sclerosis;

Early signs are fasciculations in individual muscles, often including the tongue, accompanied by mixed flaccid and spastic paresis and muscular atrophy

Bulbar dysfunction is manifested by difficulties with speech and swallowing

Some patients experience compulsive laughter or crying

CLINICAL Symptoms and Signs

Difficulty in swallowing, chewing, coughing, breathing, and talking (dysarthria) occurs with bulbar involvement.

The disorder is progressive, and ALS is usually fatal within 3–5 years; death usually results from pulmonary infections.

Patients with bulbar involvement generally have the poorest prognosis, while patients with primary lateral sclerosis often have a longer survival despite profound quadriparesis and spasticity.

Differential diagnosis

Clinical manifestation in the early stage of ALS are similar to those of spinal muscular atrophy, cervical myelopathy, and other motor system diseases

These conditions can be excluded by further testing

Often the subtle initial changes can be detected only by MRI follow-up

Wallerian degeneration, Hypertrophic Olivary Degeneration, Metabolic Diseases involving bilateral CSTs, Demyelinating and Inflammatory Diseases,

Neoplasms: Brainstem Glioma, and Malignant Lymphoma

General Features

- Best diagnostic clue
  - Bilateral hyperintensities along CST extending from corona radiata to brainstem on T2WI/PD/FLAIR
- Location
  - Hallmark is CST and LMN degeneration
    - LMN in anterior horn of spinal cord and brainstem
    - Corticospinal UMN in precentral gyrus (motor cortex)
  - White matter (WM) and gray matter (GM)
  - Frequently, prefrontal motor neurons involved in planning or orchestrating work of UMN and LMN
- Size
  - Atrophy of motor system, particularly pyramidal tract, in advanced stages of ALS
- Morphology
  - Oval or thin curvilinear hyperintensities conforming to CST

Conventional Magnetic Resonance Imaging

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Conventional Magnetic Resonance Imaging

MRI is the most sensitive imaging modality for detecting neurodegenerative changes in the CNS

The degenerative process usually leads to scarring and atrophy

This is manifested by faint signal changes and a decrease in brain volume

Conventional Magnetic Resonance Imaging

Conventional magnetic resonance imaging (MRI) is routinely used to look for other pathologies, such as cerebral mass lesions, multiple sclerosis, cervical spondylotic myelopathy, conus lesions, or lumbosacral radiculopathy.

In patients with ALS, a few subtle changes have been reported on T1-weighted, T2-weighted, proton density, and fluid-attenuated inversion recovery images (FLAIR), which are not diagnostic but are supportive of the diagnosis of a MND in patients with high clinical suspicion.

Conventional Magnetic Resonance Imaging

Hyperintensities of the corticospinal tract (CST) in ALS have been reported by some as best detected on T2-weighted images and by others as best seen on proton density or FLAIR sequences.

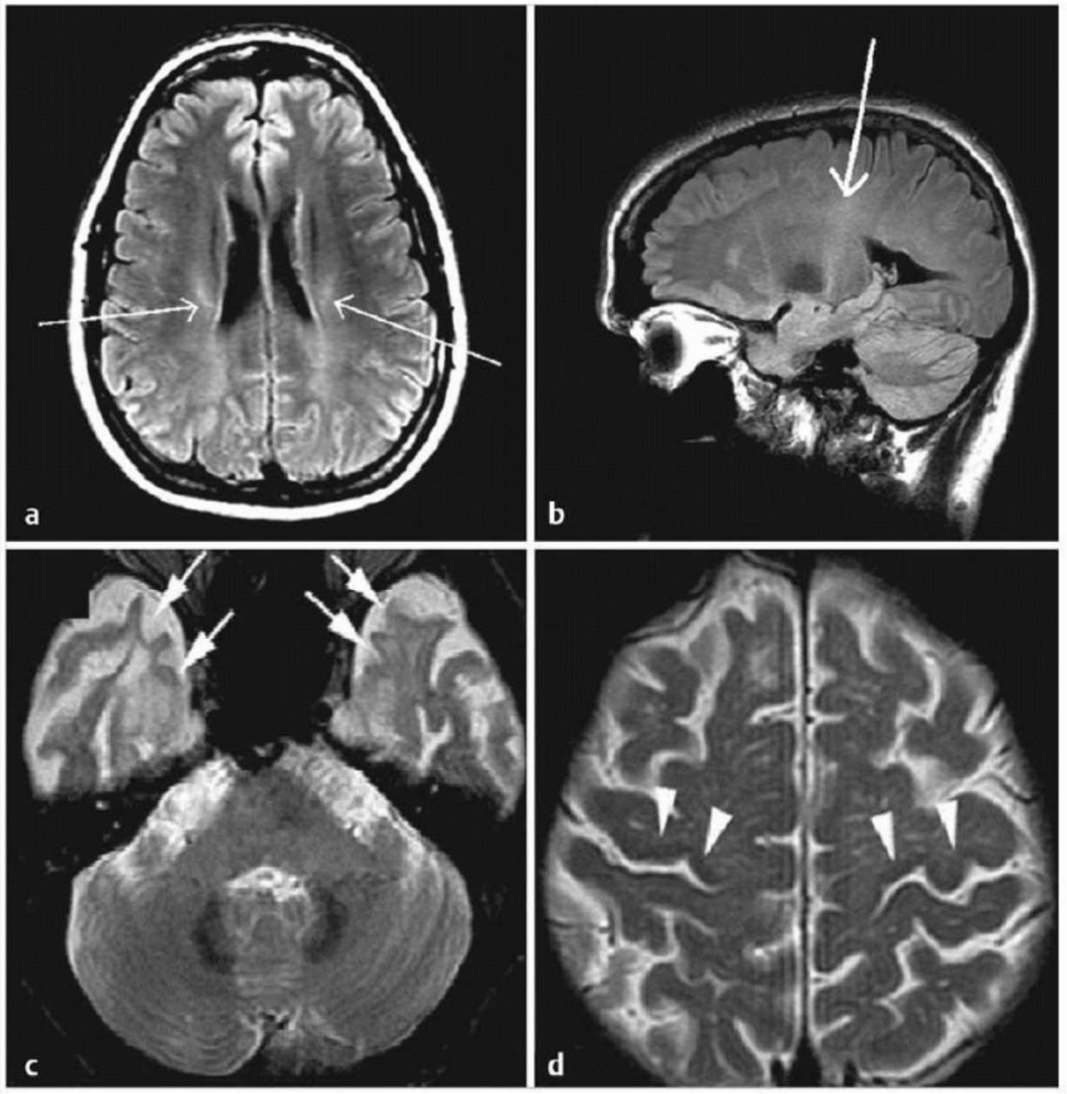
They are most readily identified in the posterior limb of internal capsule and are best monitored on the coronal images from centrum semiovale to the brainstem.

Increased T2 signal is also seen in the extramotor frontotemporal regions.

The precentral cortex can appear as a hypointense rim on T2- weighted and FLAIR images in patients with ALS.

a,b) 43-year old woman with ALS

c,d) 58-year-old patient with ALS with dementia



BUT

The mechanism has been thought to be a T2 shortening effect that results from excessive iron accumulation, fibrillary gliosis, or macrophage infiltration, but this is neither specific nor sensitive for ALS pathology.

Hyperintensity of the anterolateral columns of the cervical cord has been observed on T2-weighted images in patients with ALS, consistent with the degeneration of the CST at autopsy, and is more specific than signal changes in the brain.

Conventional Magnetic Resonance Imaging

There is no relationship between the degree of CST hyperintensity and the severity of clinical UMN involvement.

Specificity for ALS is not high/ Sensitivity close to 62%!

Conventional Magnetic Resonance Imaging

A recent study with 7 T MRI revealed similar T2 hyperintensities in bilateral lateral segments of the spinal cord.

Magnetic Resonance Imaging Finding

Consistent with the underlying process of motor neuron degeneration with gliosis and demyelination, T2w images show hyperintensity along the pyramidal tract in the corona radiata, internal capsule, cerebral peduncles, and in the brainstem

Other possible findings are atrophy and reduced volume of the pyramidal tract and narrowing of the spinal cord

Asymmetrical atrophy of the tongue muscles may occur as an incidental finding

Imaging Finding

Small percentage demonstrate CST hyperintensity

As CST is normally slightly hyperintense, especially at 3.0 T, this finding lacks sensitivity & specificity

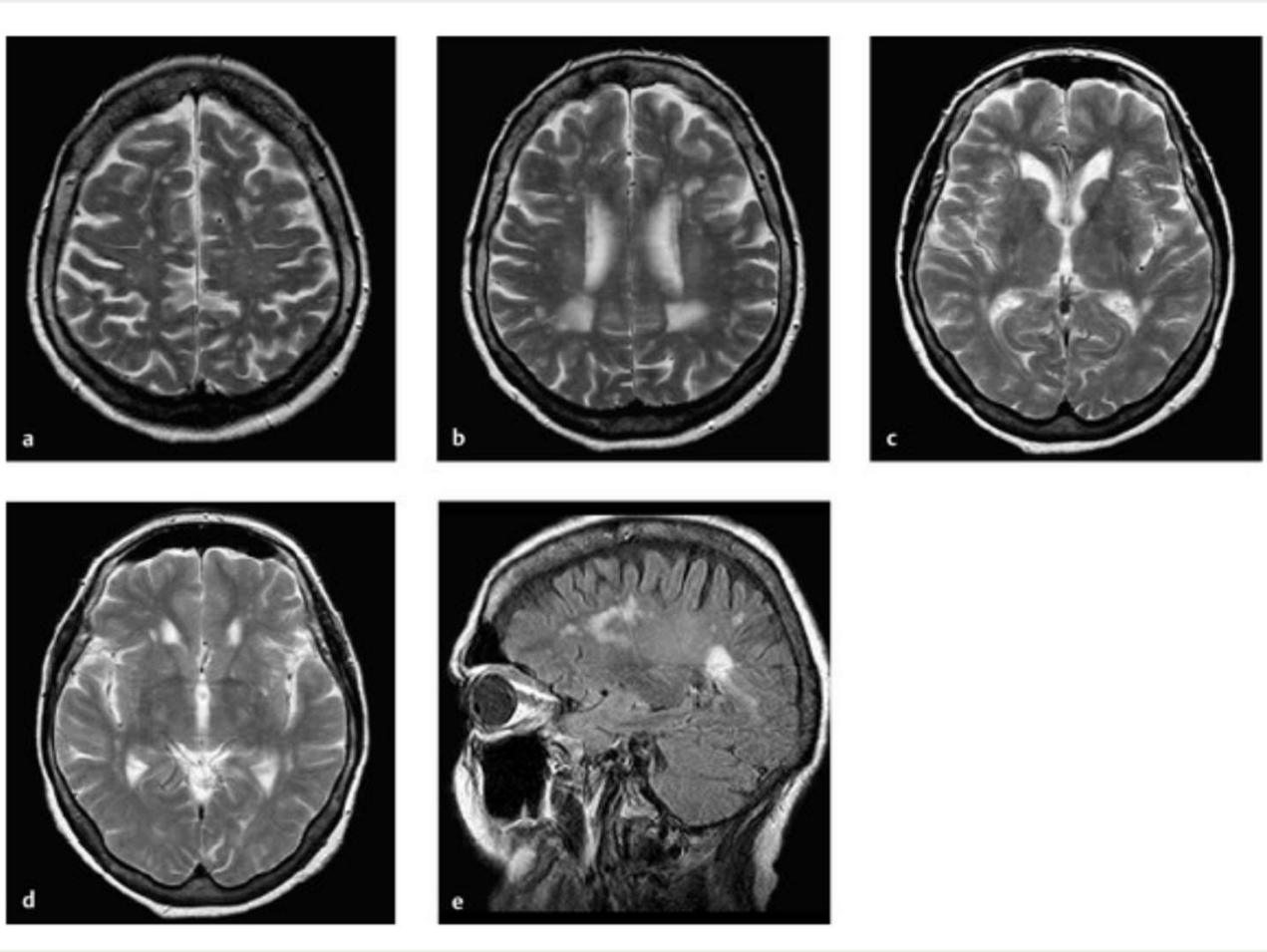
T2 hyperintense CST may be specific for ALS

when seen on corresponding proton density (PD) images

DWI hyperintensity (↓ diffusivity) in CST

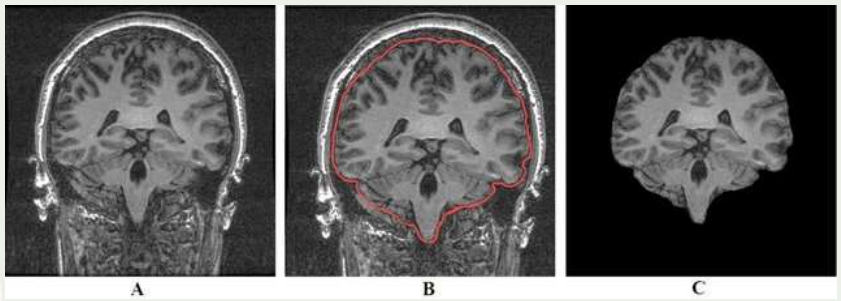
Hypointense gray matter in precentral gyrus (motor cortex)

Note: Consider FLAIR and PD in suspected ALS


a
b
c
d
e

Signal intensity changes seen on T2W, fluid-attenuated inversion recovery (FLAIR) and proton density (PD)-weighted sequences are not sensitive or specific in ALS, although their presence may be reflective of different pathologies and may assist in differential diagnosis.

These sequences were included to assess for co-existing disease and to be available for image processing pipelines (e.g., skull stripping) that some investigators may employ.



Voxel-Based Morphometry

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Voxel-Based Morphometry

Voxel-based morphometry (VBM) is an automated statistical approach that is used to detect the regional differences in brain tissue density and tissue amount.

The technique typically uses T1-weighted volumetric MRI scans and performs statistical tests across all voxels in the image to identify volume differences between groups.

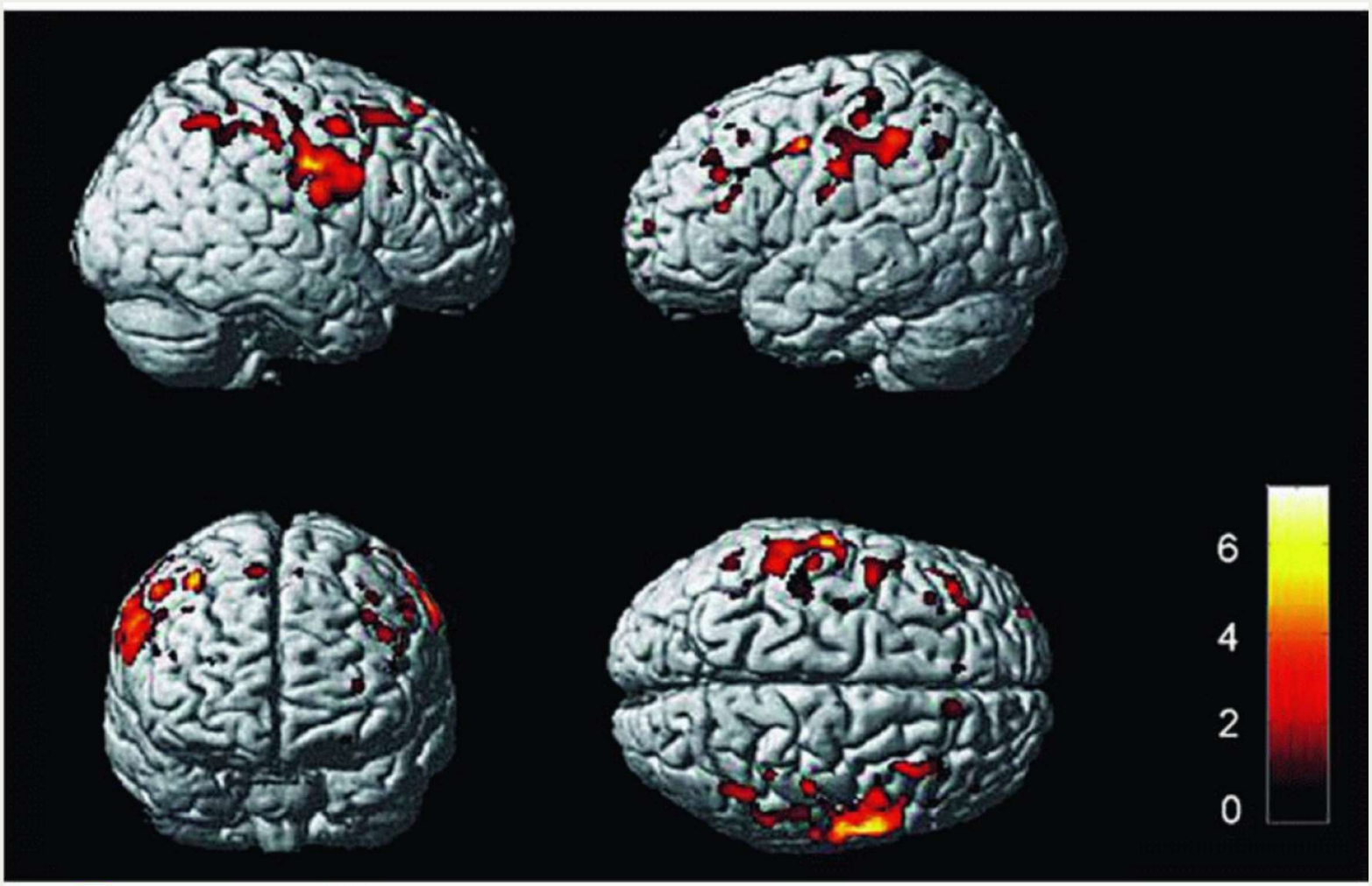
Voxel-Based Morphometry

Global atrophy, as noted by reduced brain parenchymal fraction (BPF) in comparison to healthy control subjects, has been reported in some studies of patients with ALS.

Regional gray matter (GM) atrophy of not only the motor cortex, but also the frontotemporal and parietal regions, has been noted in patients with ALS without cognitive impairment.

Atrophy of the frontal regions has been noted to be severe in patients with ALS and frontotemporal dementia (FTD).

ALS patients with mild cognitive impairment without evidence of frank FTD have also demonstrated gray matter loss in the frontal, parietal, and limbic regions compared with patients with no cognitive loss.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Voxel-Based Morphometry

VBM studies have also provided evidence of white matter (WM) atrophy in extramotor areas, such as the corpus callosum, cerebellum, frontotemporal and occipital regions, supporting the theory that ALS is a multisystem disease and suggesting that extramotor involvement may be seen early in the disease.

A few longitudinal studies have looked at the progression of GM loss and have demonstrated greater GM atrophy in the motor and extramotor frontal regions with disease progression, more pronounced in rapidly progressing cases.

Magnetic Resonance Spectroscopy

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Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a noninvasive technique to evaluate the chemical environment of the brain. Because Nacetyl aspartate (NAA) is primarily found in neurons, whereas creatine (Cr) and choline (Cho) can be derived from all brain cells, the absolute concentration of NAA and the NAA/Cr and NAA/Cho ratios are considered markers of neuronal structural integrity.

MRS studies can be performed from a single voxel using a single-voxel spectroscopy technique or using a chemical-shift imaging technique in which multiple voxels can be studied simultaneously.

Magnetic Resonance Spectroscopy

Proton MRS studies reveal reduced concentrations of NAA or reduced NAA:Cr, NAA:Cho, and NAA:Cr+Cho ratios in the motor cortex in ALS.

Magnetic Resonance Spectroscopy

These changes are most prominent in the precentral gyrus and the corona radiata, but they can also be seen in the premotor regions, primary sensory cortex, and extramotor frontal regions, with relative sparing of the parietal lobes.

Similar changes are also seen in the brainstem, primarily in the pons and upper medulla of patients with prominent UMN or bulbar signs.

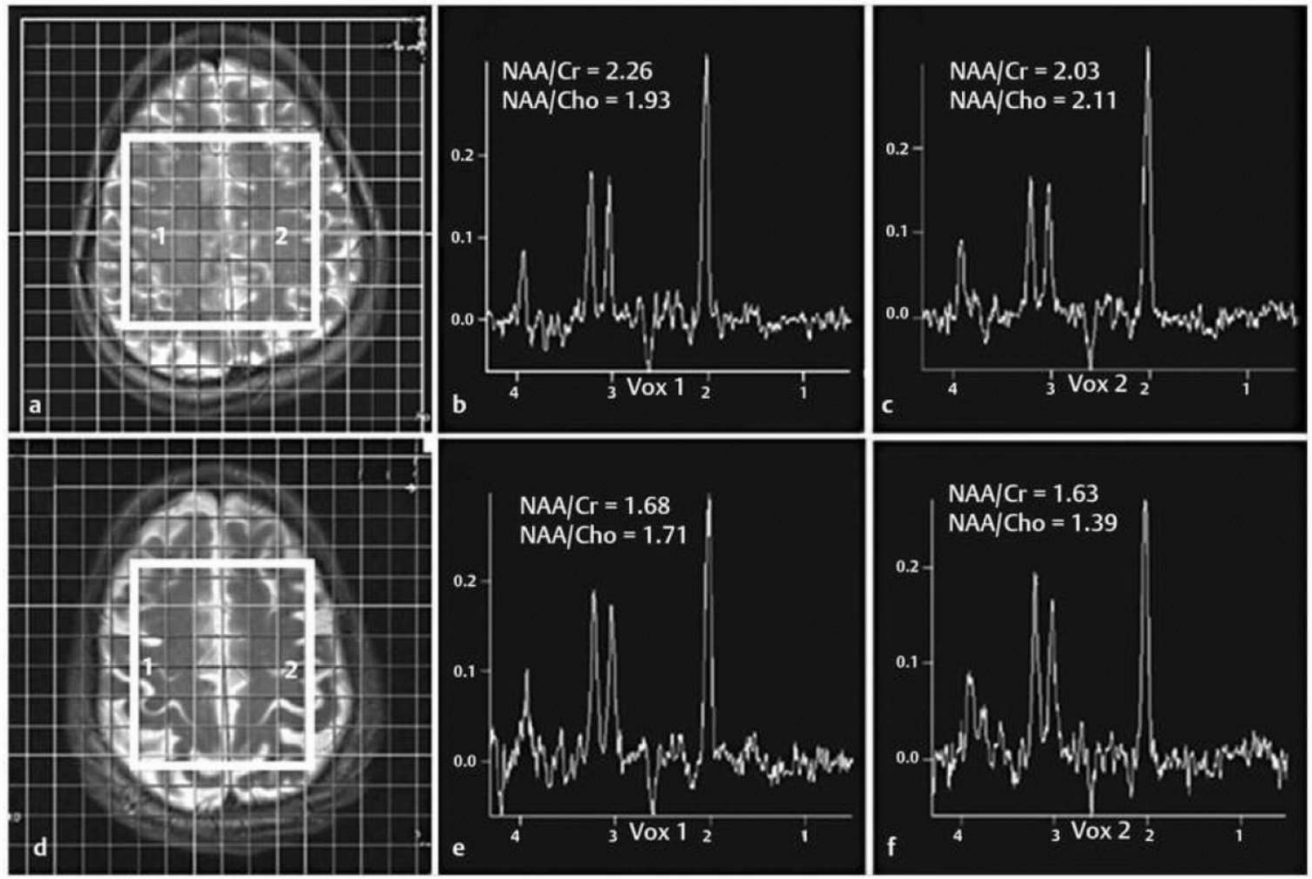
Magnetic Resonance Spectroscopy

Reduced concentrations of NAA correlate with disease severity in patients with ALS as measured with the ALS Functional Rating Scale-Revised and with UMN signs.

Bulbar onset patients tend to have a lower NAA:Cr + Cho ratio than limb onset patients, and the frontal NAA:Cr ratio correlates well with cognitive dysfunction.

Myo-inositol, another spectroscopic biomarker for glial activity, is also noted to be increased in the motor cortices of patients with ALS.

Magnetic Resonance Spectroscopy



2D multivoxel spectroscopy of the motor cortex in a control subject (a-c) and a patient with ALS patient (d-f).
Axial T2-weighted image shows the grid and the volume of interest.

Diffusion Tensor Imaging

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Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is a relatively new MR-based technique that allows estimation of the orientation of white matter fiber bundles based on the diffusion characteristics of water.

This technique permits the detection of brain injuries earlier than they can be detected by conventional imaging techniques.

Diffusivity of water is generally higher along the direction of the fiber tracts than perpendicular to them.

Diffusion Tensor Imaging

A quantitative measure of the overall presence of obstacles to diffusion is called mean diffusivity (MD).

The MD is a measure of diffusivity of water molecules irrespective of the direction and hence is higher in less restricted environments, such as cerebrospinal fluid.

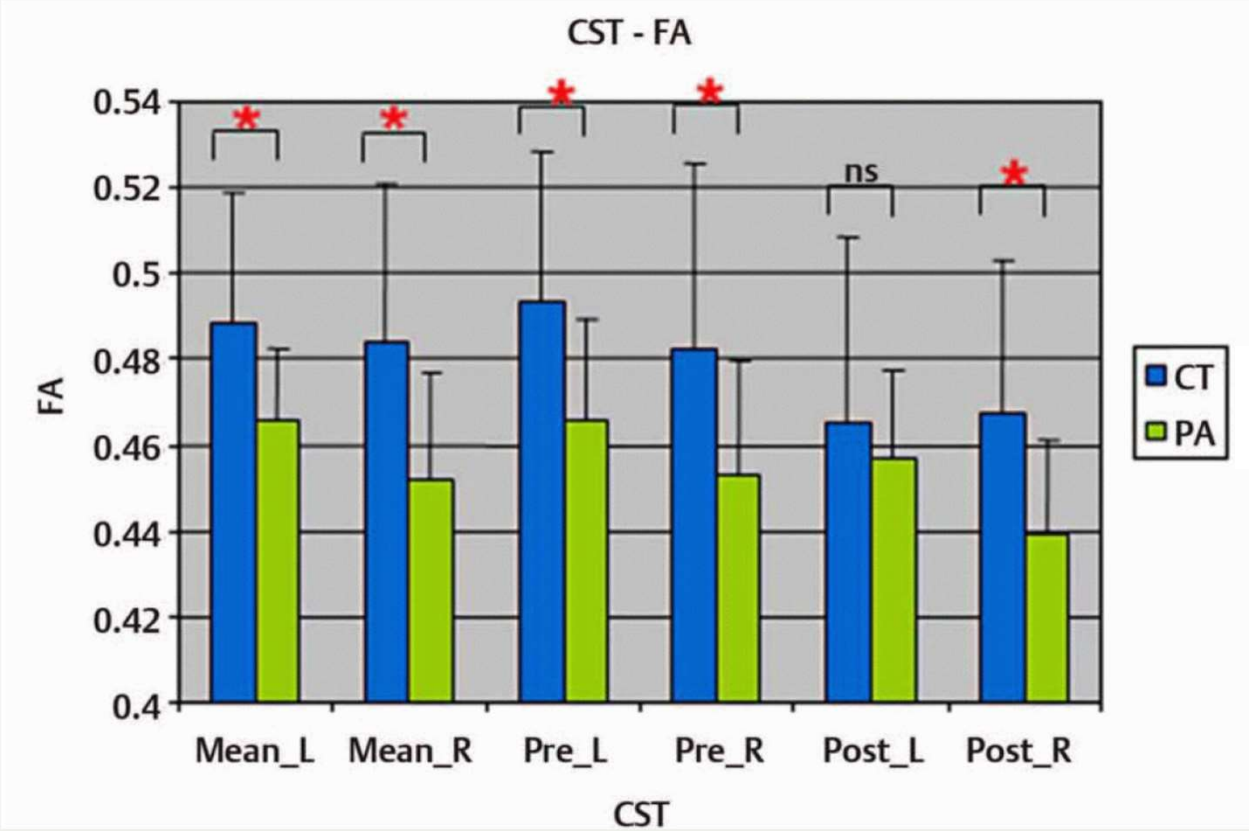
The directionality of diffusion can be quantified by fractional anisotropy (FA), which ranges from zero (no directional dependence of diffusion) to one (diffusion along a single direction).

Thus, any structural change in the white matter or axonal loss would affect the diffusion characteristics and lead to an increase in the MD and a decrease in FA.

Diffusion Tensor Imaging

Increased MD and decreased FA along the CST have been reported in multiple studies as a measure of UMN dysfunction in patients with ALS.

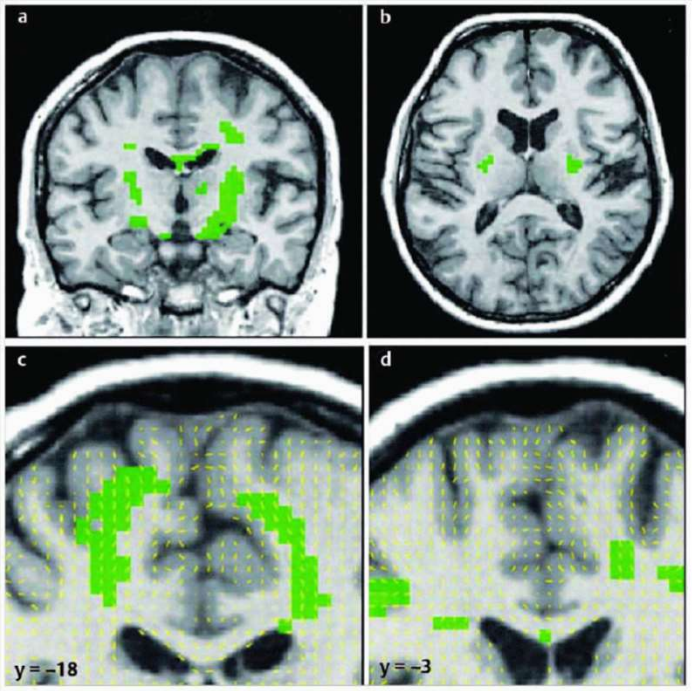
Diffusion Tensor Imaging



26 healthy controls (blue)
28 ALS patients (green)

Diffusion Tensor Imaging

Patients with bulbar-onset ALS have the most significant decrease in FA



Reduced fractional anisotropy in the pyramidal tract, corpus callosum, and thalamus (a,b), and under the motor and premotor cortex (c,d)

Diffusion Tensor Imaging

Decreased FA has been correlated with severity and disease progression in ALS patients in some studies, but other studies have failed to confirm this finding.

Diffusion Tensor Imaging

Cervical cord FA has been reported to be decreased in patients with ALS compared with controls and to correlate with disease severity.

Longitudinal follow-up of these patients demonstrates a significant decrease in the cord FA and an increase in the MD over time, despite the stability of the brain CST FA and MD.

DTI studies recorded with a voxel-based approach also have shown extramotor involvement in the corpus callosum, premotor white matter, prefrontal white matter, and temporal regions.

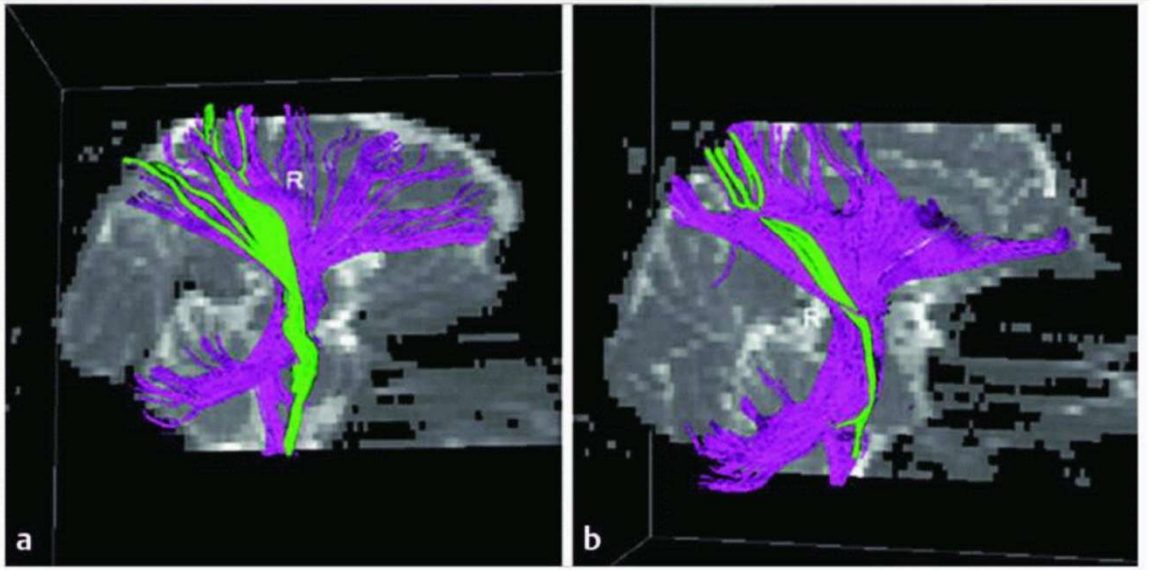
Diffusion Tensor Imaging

Diffusion tensor imaging also allows interregional fiber tracking. Known as diffusion tensor tractography,

This technique allows identification of major white matter tracts as they course through the brain.

Further quantification of the white matter tracts can be performed using a region-based approach.

Diffusion Tensor Imaging



Diffusion tensor tractography of a control subject (a) compared with patient with ALS (b).

Functional Magnetic Resonance Imaging

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Functional Magnetic Resonance Imaging

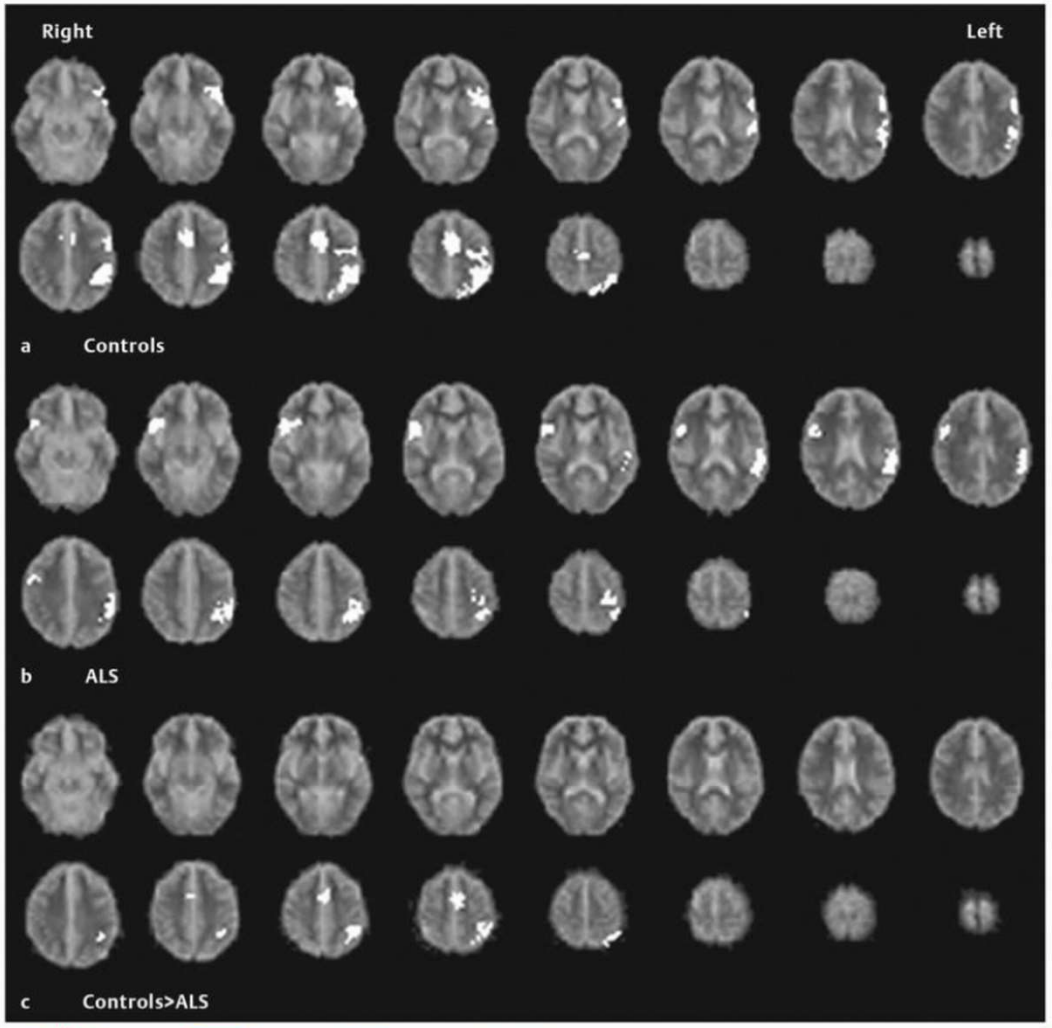
Functional MRI (fMRI) is a noninvasive tool based on the blood oxygen-dependent contrast method, relying on the T2 effect of deoxyhemoglobin in the tissues.

Patients with ALS have been noted to demonstrate increased activation of the premotor cortex, supplementary motor area, basal ganglia, and cerebellum during simple motor tasks, such as finger tapping.

Functional Magnetic Resonance Imaging

fMRI studies during a motor imagery task also revealed increased activation of the premotor areas, a finding that became more prominent with longer disease duration.

Another fMRI study of ALS patients during motor imagery tasks revealed reduced activation of the parietal and medial frontal regions, areas that are usually involved in motor imagery tasks. This finding suggests reduced activation of the usual networks, possibly related to involvement of the prefrontal cortex by the underlying disease



Functional magnetic resonance imaging demonstrating areas of activation during motor imagery in healthy controls (a) and in ALS patients (b).

Functional Magnetic Resonance Imaging

Impaired activation of the middle and inferior frontal gyri, anterior cingulate gyrus, and the parietal and temporal lobes has been demonstrated in ALS patients during letter fluency and confrontation naming tasks, corresponding to clinical deficits in these spheres by the patients.

Functional Magnetic Resonance Imaging

Resting-state fMRI measures fluctuations in the blood oxygen level dependent (BOLD) signal in the brain when the participant is not occupied with any task-based stimuli;

thus identifying potential abnormal functioning of resting-state networks (RSNs).

In ALS, the sensorimotor network (SMN) and default mode network (DMN) have altered functional connectivity in both motor and non-motor regions.

Susceptibility Weighted Imaging

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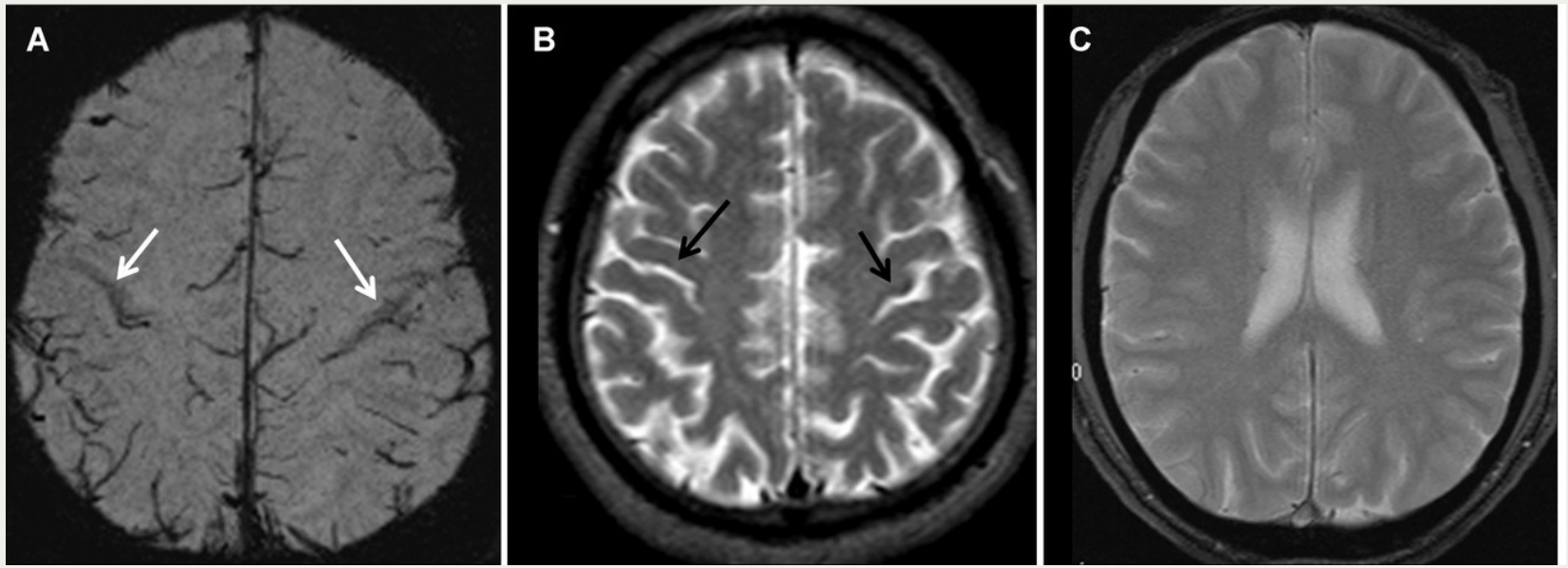
Susceptibility Weighted Imaging

The SWI sequence exploits tissue magnetic susceptibility differences to generate unique and enhanced contrast images such as R2* and quantitative susceptibility maps (QSM), providing an objective measure of cerebral iron accumulation.

Past SWI studies in ALS have revealed signal abnormalities suggesting abnormal iron metabolism or deposition diffusely in WM and the motor cortex.

Texture analysis applied to SWI images has demonstrated alterations within the precentral gyrus and basal ganglia.



(A) Axial SWI of a superior slice shows markedly low signal intensity in bilateral precentral cortices compared to the superior frontal cortices.

(B) Axial conventional T2-weighted image of a superior slice shows mildly low intensity in bilateral precentral cortices compared to the superior frontal cortices of the same slice.

(C) Axial T2*-weighted image of superior slice appears isointense compared to superior frontal cortices.

Magnetization Transfer Imaging

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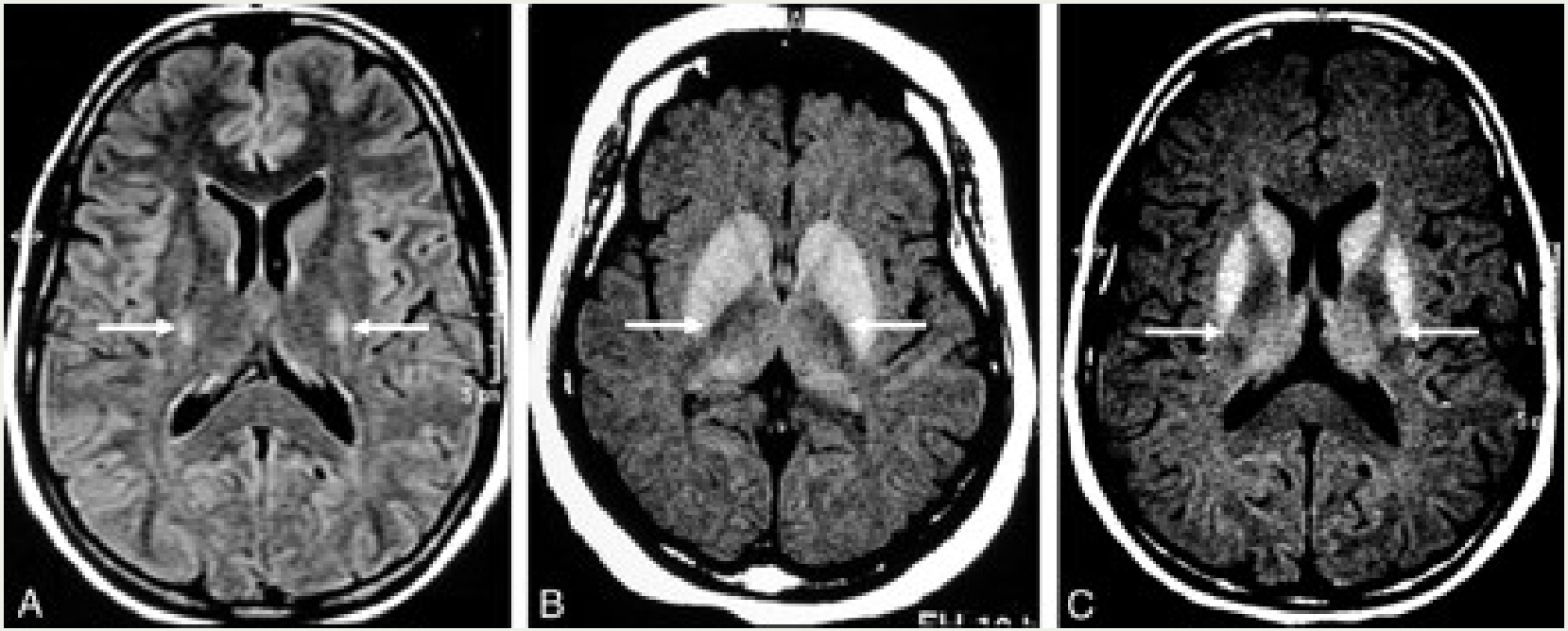
Magnetization Transfer Imaging

Magnetization transfer ratio (MTR) is an MR-based parameter that measures the exchange of magnetization between free protons (water molecules) and those bound to macromolecules and is thus thought to reflect alterations in macromolecular structures.

Reduced MTR values are indicative of inability of neuronal macromolecules to exchange magnetization with the surrounding free water molecules, which correlates with axonal degeneration and demyelination.

MT imaging also improves the visibility of gadolinium-enhancing lesions by suppressing the surrounding normal brain parenchyma and leading to contrast augmentation.



MR images of the CST in the internal capsule

A and B, Control subject. Hyperintensity on FLAIR image (arrows in A) and hypointensity on T1-weighted SE MTC image (arrows in B) in the region of the CST in the internal capsule.

C, Patient with definite ALS. Pathologic hyperintensity (arrows) in the same region on a T1-weighted SE MTC image.

Summary of MRI Findings

T1-W

- Different T1 appearances of CST
  - Isointensity (most common) may reflect ↑ content of free radicals
  - Hypointense or mild hyperintense signal
  - CST differs between ALS patients and normal subjects only at internal capsule

- **T2-W**

○ Small percentage demonstrate CST hyperintensity

○ Hyperintensity can occur anywhere from subcortical white matter of precentral gyrus to posterior limb internal capsules, cerebral peduncles, & pons

○ As CST is normally slightly hyperintense especially at 3.0 T, this finding lacks sensitivity & specificity

○ T2 hyperintense CST may be specific for ALS when seen on corresponding PD images

○ Hypointense GM in precentral gyrus (motor cortex)

– Nonspecific; may be due to iron and heavy metals accumulation in cortex of aged patients

- **PD/intermediate**

○ Hyperintense CST

• FLAIR

○ More sensitive and less specific than T2 FSE for detecting hypointensity in precentral gyrus

○ Hyperintense CST

– More frequently seen on FLAIR than on T2/T1/PD

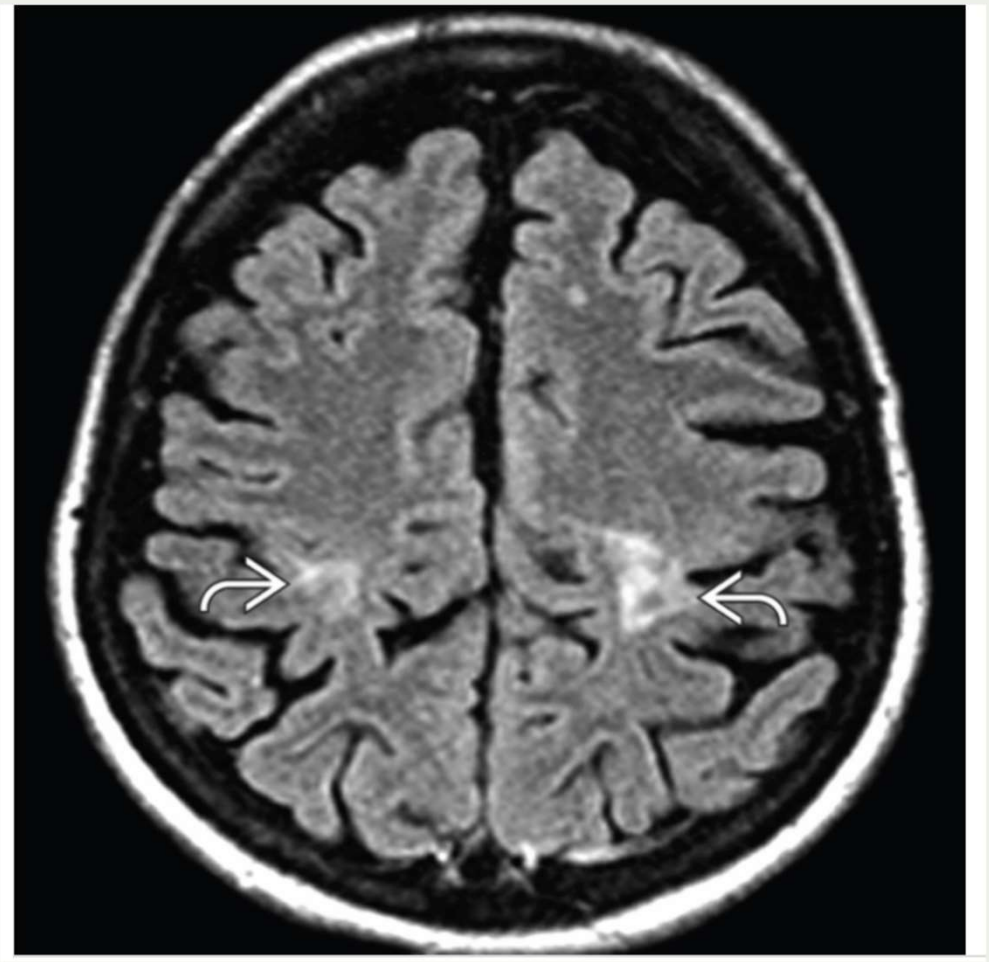
- **DWI**
  - Hyperintensity in CST
    - May be seen in the absence of T2 hyperintensity
- Diffusion tensor imaging (DTI)
  - ROI-based approaches & tractography demonstrates significant changes in diffusion parameters along CST
  - Most common finding: ↓ fractional anisotropy (FA) in CST due to neuronal degeneration of UMN
  - FA ↓ demonstrated at all levels of CST; most significant reduction in posterior limb internal capsule
  - FA correlates with UMN involvement, disease severity
  - ↑ mean diffusivity (MD) along CST
  - MD more constant over different levels of CST; tends to be elevated at cranial level of CST
    - MD positively correlates with disease duration

- **^{1}H-MRS** useful for assessing UMN involvement
  - ↓ NAA, ↓ NAA/Cr, ↓ NAA/Cho, & ↓ NAA/(Cr + Cho) in motor cortex
  - NAA present primarily in neurons; these metabolic changes reflect loss or dysfunction of motor neurons
  - ↓ NAA/Cr & NAA/Cho ratio along CST; most pronounced in precentral gyrus & corona radiata
  - ↓ NAA in pons & upper medulla in patients with prominent UMN or bulbar signs
  - ↑ Cho in posterior limb internal capsule
  - ↑ myo-inositol in motor cortex

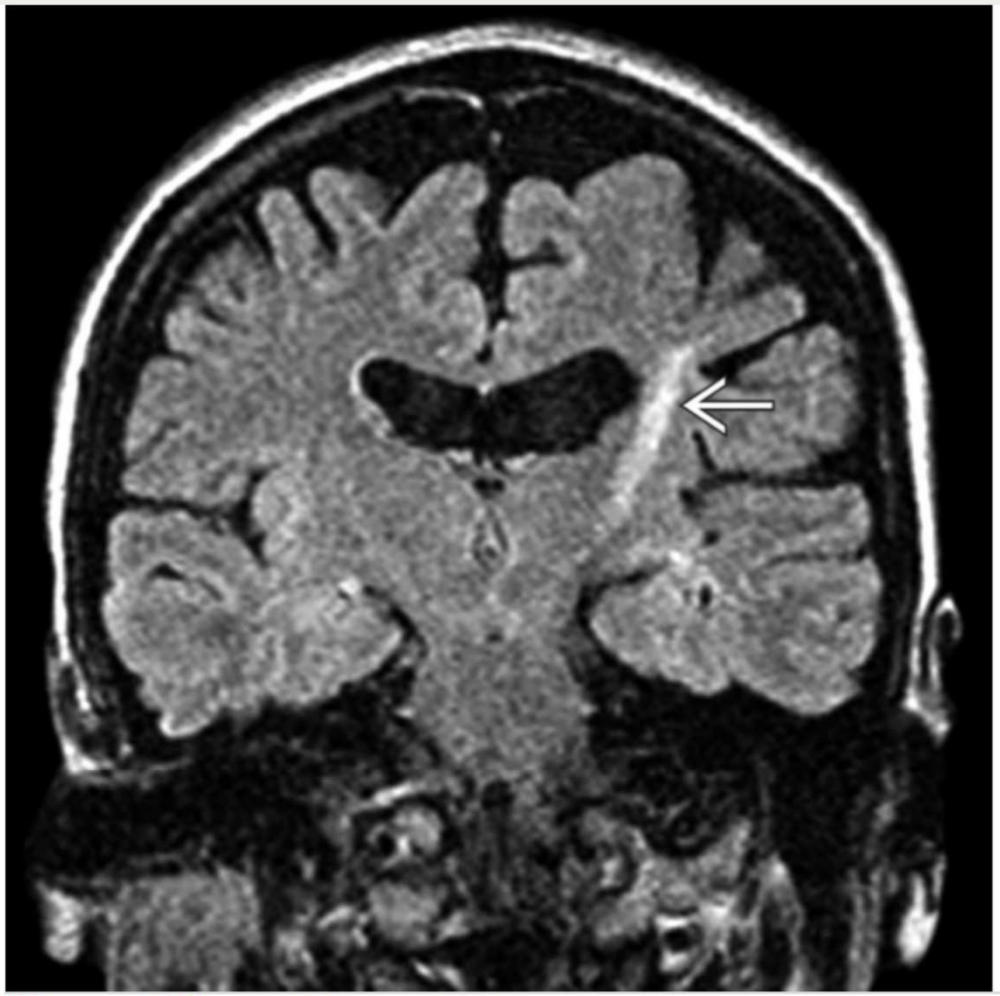
- **Magnetization-transfer ratio (MTR)** measurements
  - ↓ MTR in posterior limb of IC in ALS
  - CST hyperintensity on T1 MT contrast-enhanced images: 80% sensitivity, 100% specificity
  - May detect CST degeneration of ALS at early stage

- **Voxel-based morphometry (VBM)**
  - Regional gray matter loss in motor cortex, frontal, temporal, parietal & limbic regions
  - Frontal severe atrophy in ALS & frontotemporal dementia
  - WM loss in corpus callosum, cerebellum, frontotemporal & occipital regions
  - Global brain atrophy relatively mild

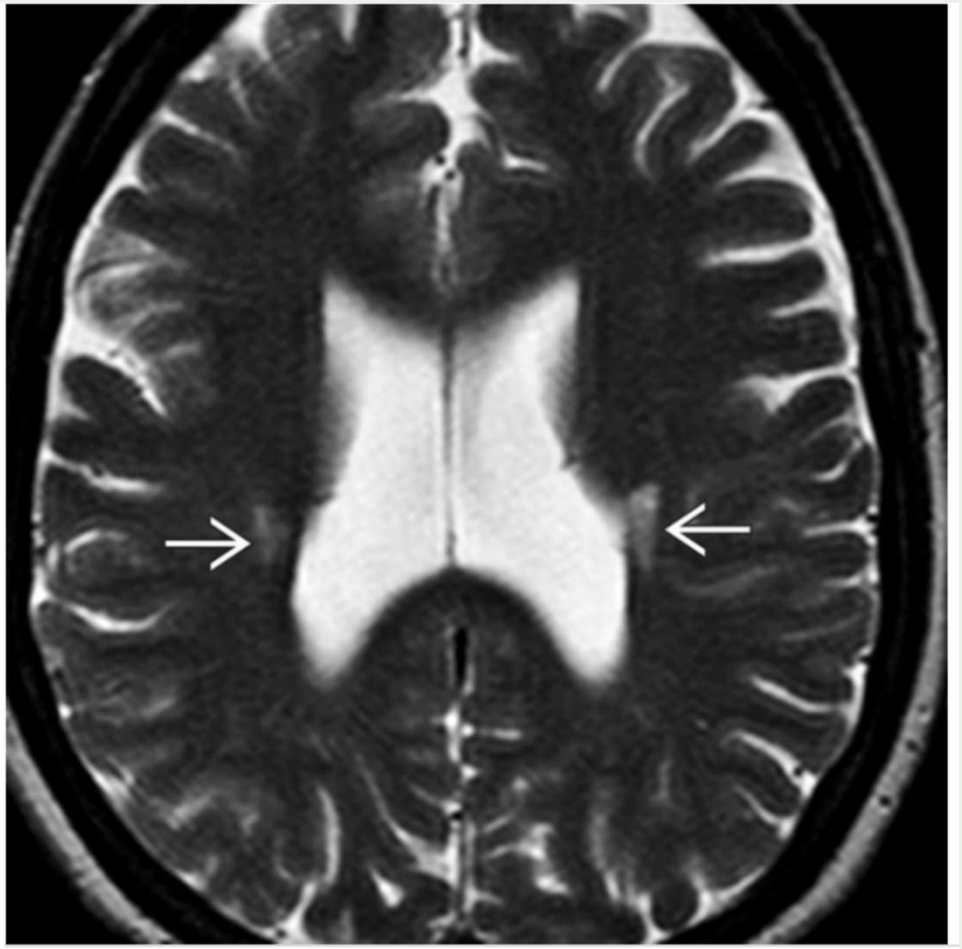
- **Functional MR**
  - Pattern of cortical reorganization
  - ↑ activation of contralateral sensorimotor cortex, supplementary motor area, basal ganglia, & cerebellum during motor tasks



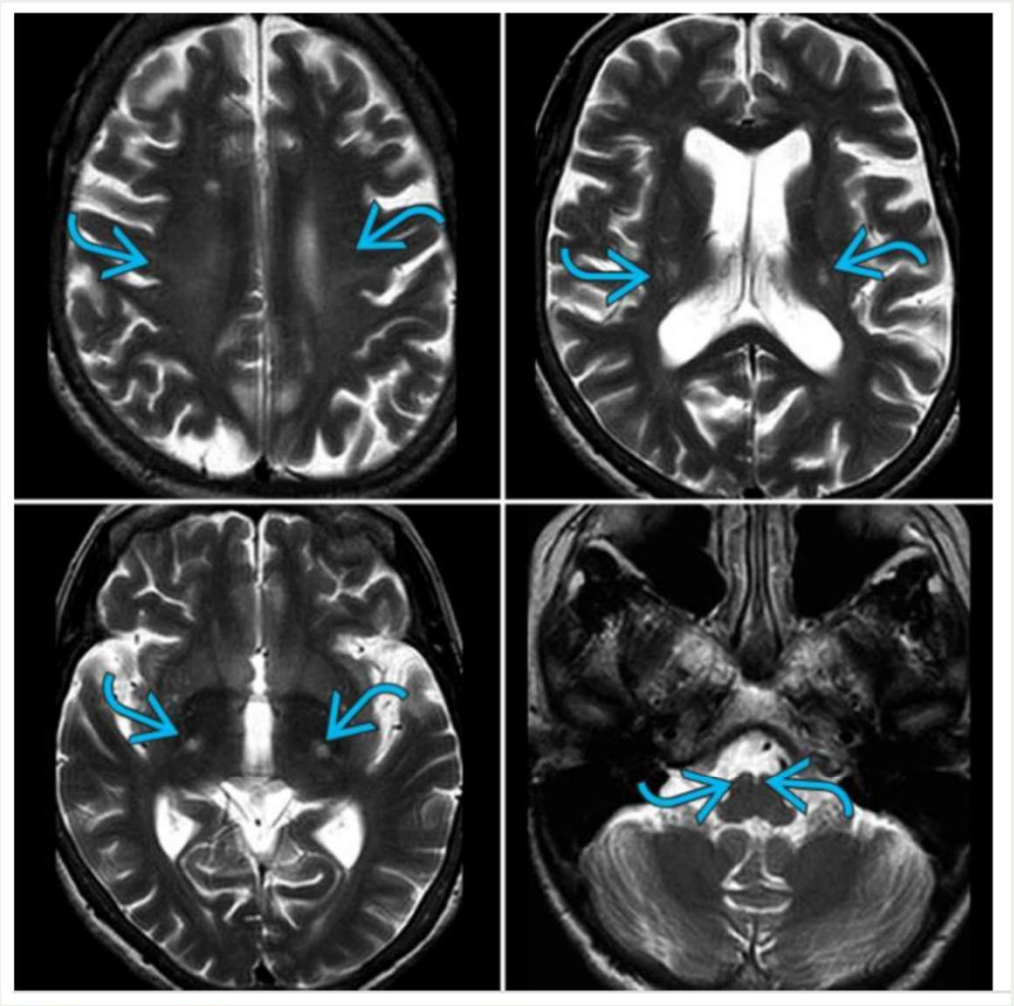
Axial FLAIR MR shows increased signal in the precentral gyri in a ALS patient. There is also atrophy of bilateral motor cortices.



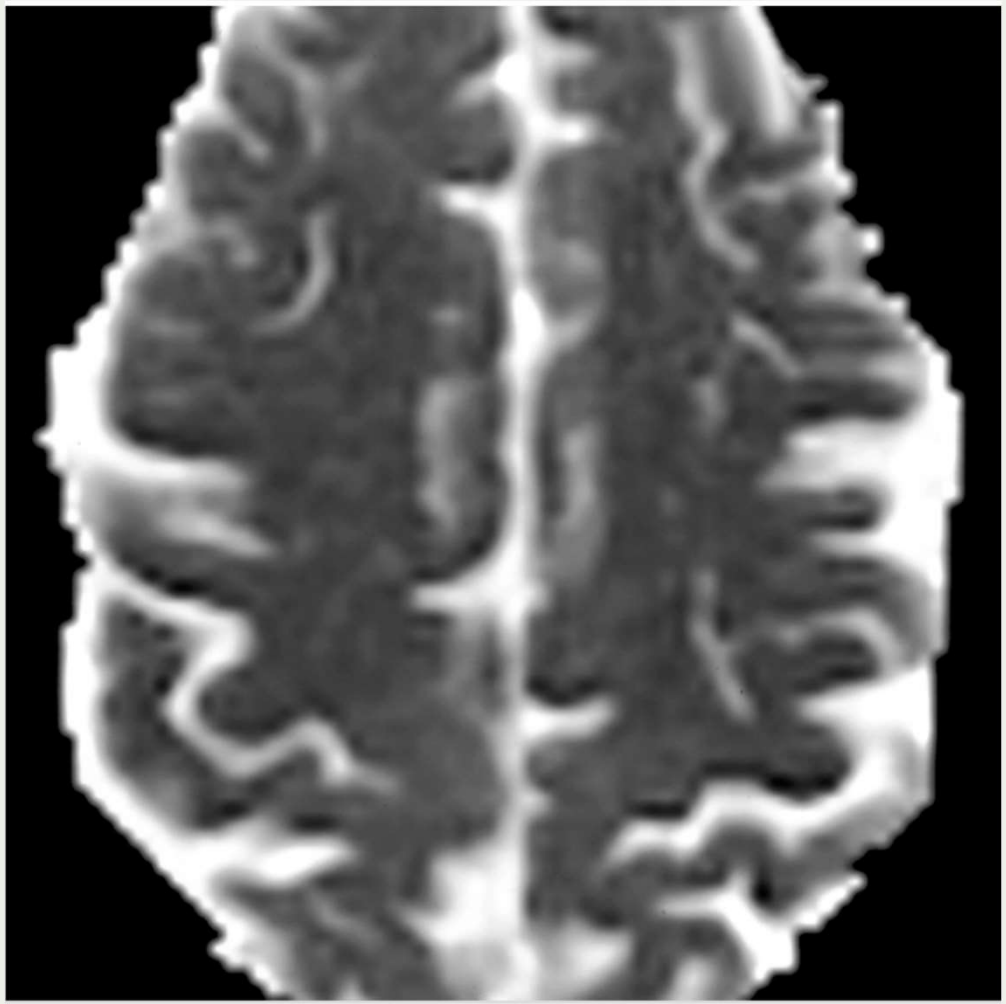
Coronal FLAIR MR shows linear hyperintensity along the CST from the precentral gyrus to the cerebri crus; right CST signal abnormality is out of this slice. Hyperintensity of the precentral gyrus subcortical WM on FLAIR is a potentially useful and specific sign of ALS not seen in healthy, asymptomatic patients.



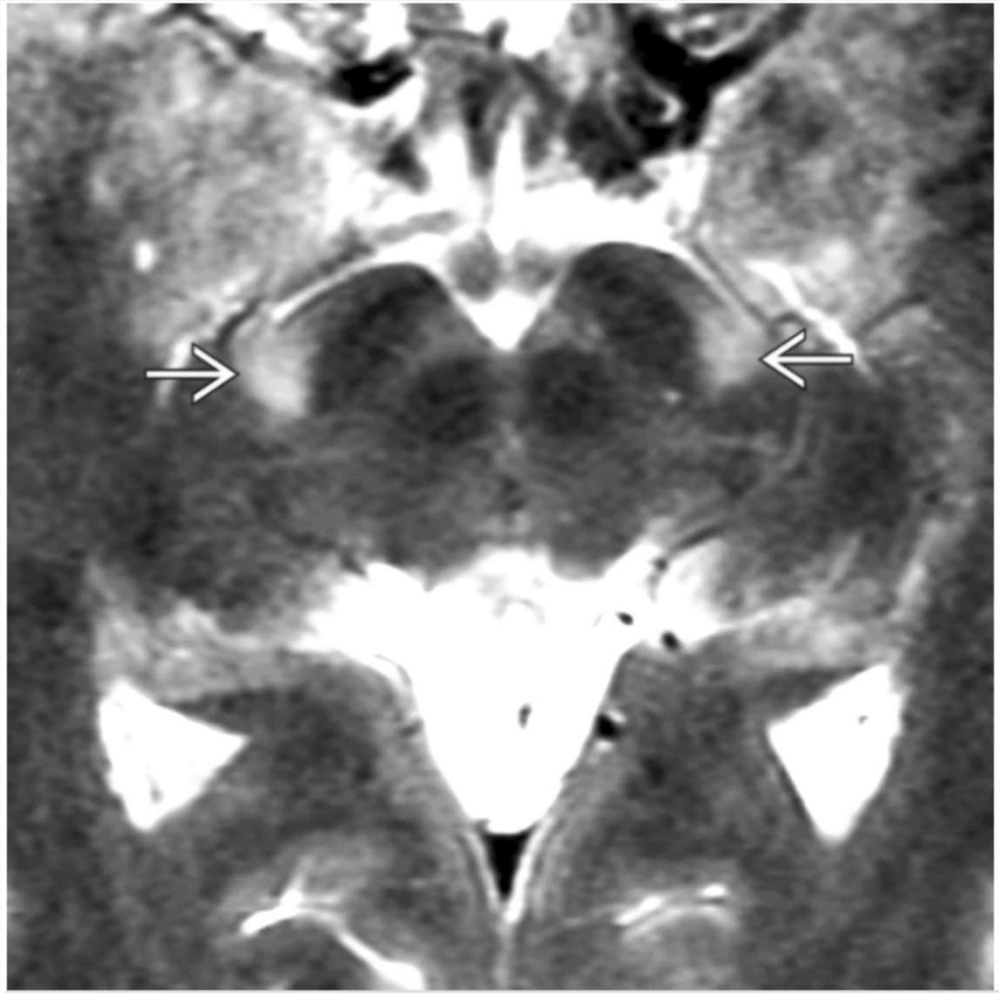
Axial T2WI FS MR demonstrates ovoid hyperintensity along the CSTs bilaterally . The atrophy and hyperintensity are due to myelin loss and gliosis. There is frequently involvement of the prefrontal motor neurons, which play a role in planning or orchestrating the work of the upper and lower motor neurons.



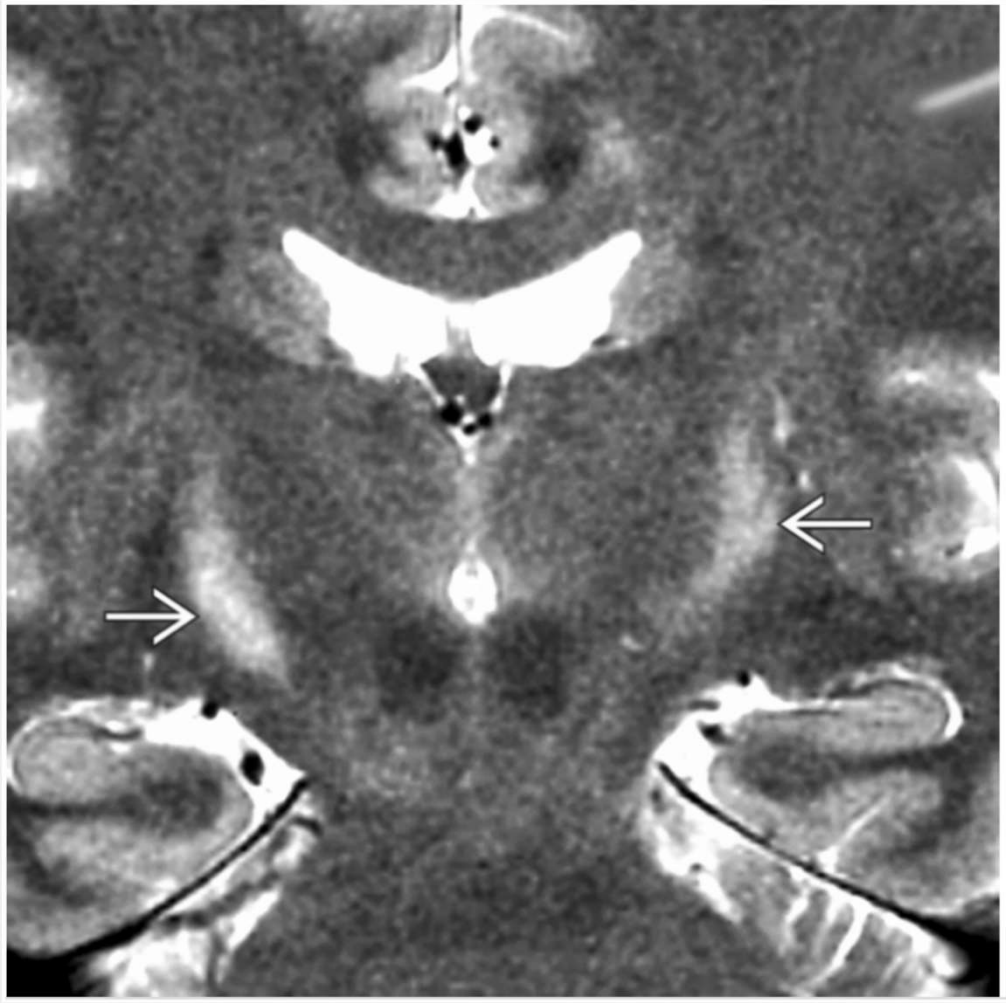
Axial T2 MR in a patient with ALS shows hyperintensity along the course of the CST bilaterally. It is important to note that CST is typically slightly hyperintense on T2, especially at 3.0 T.



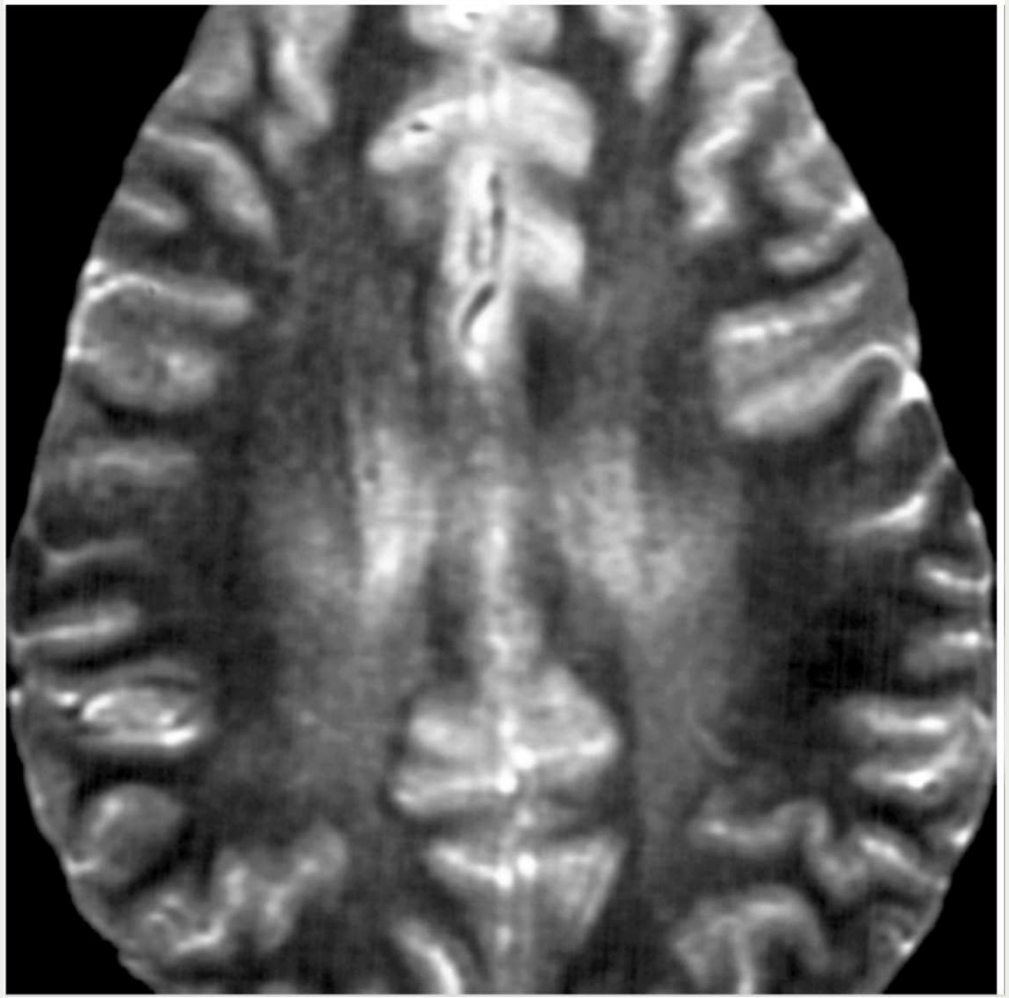
Axial ADC map in the same ALS patient appears normal.



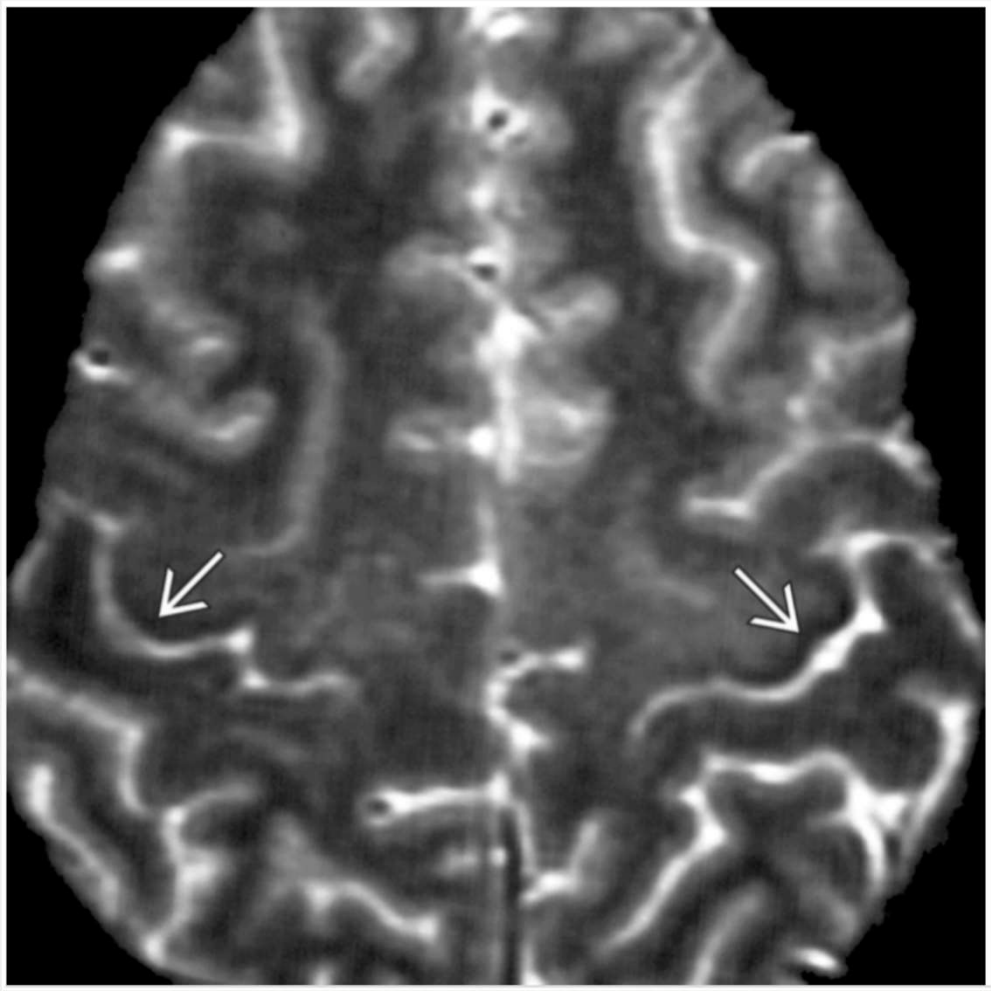
Axial T2WI MR in the same patient shows hyperintense corticospinal tracts at the level of the cerebral peduncle.



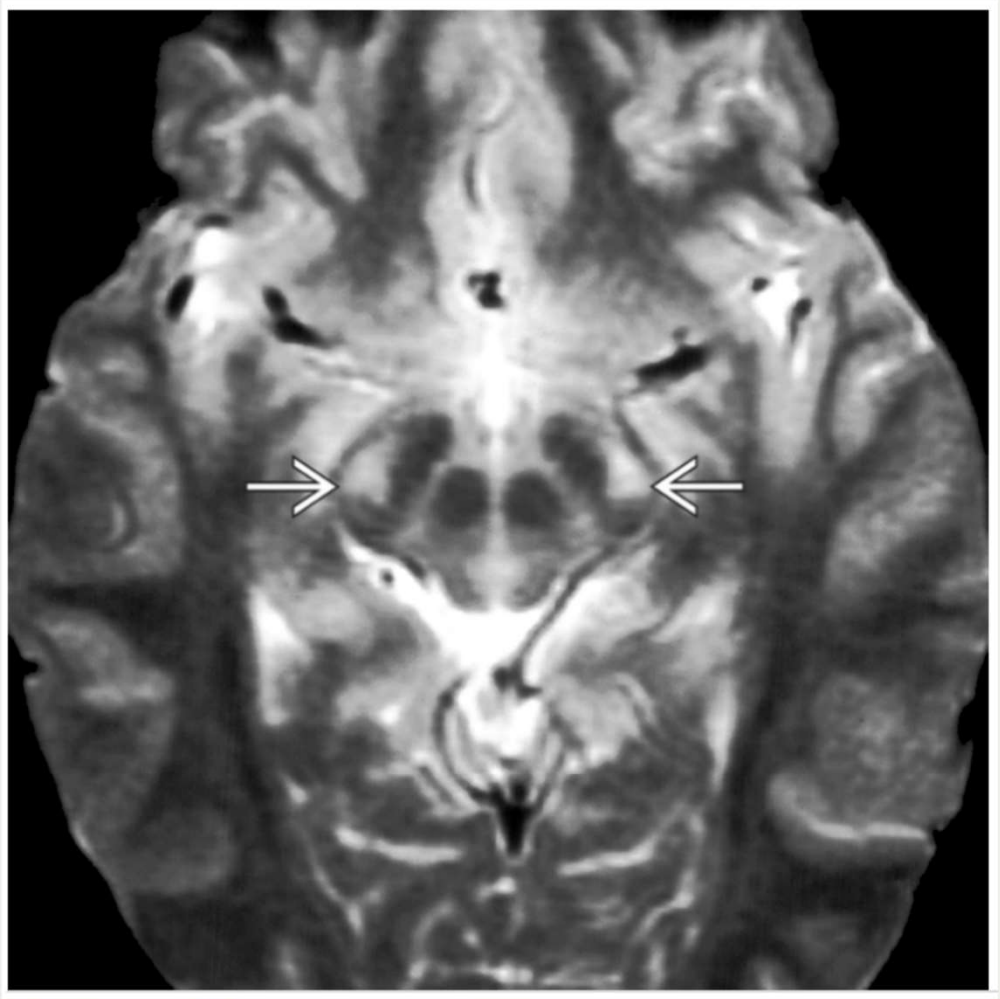
Coronal T2WI MR shows hyperintense corticospinal tracts in a patient with ALS.



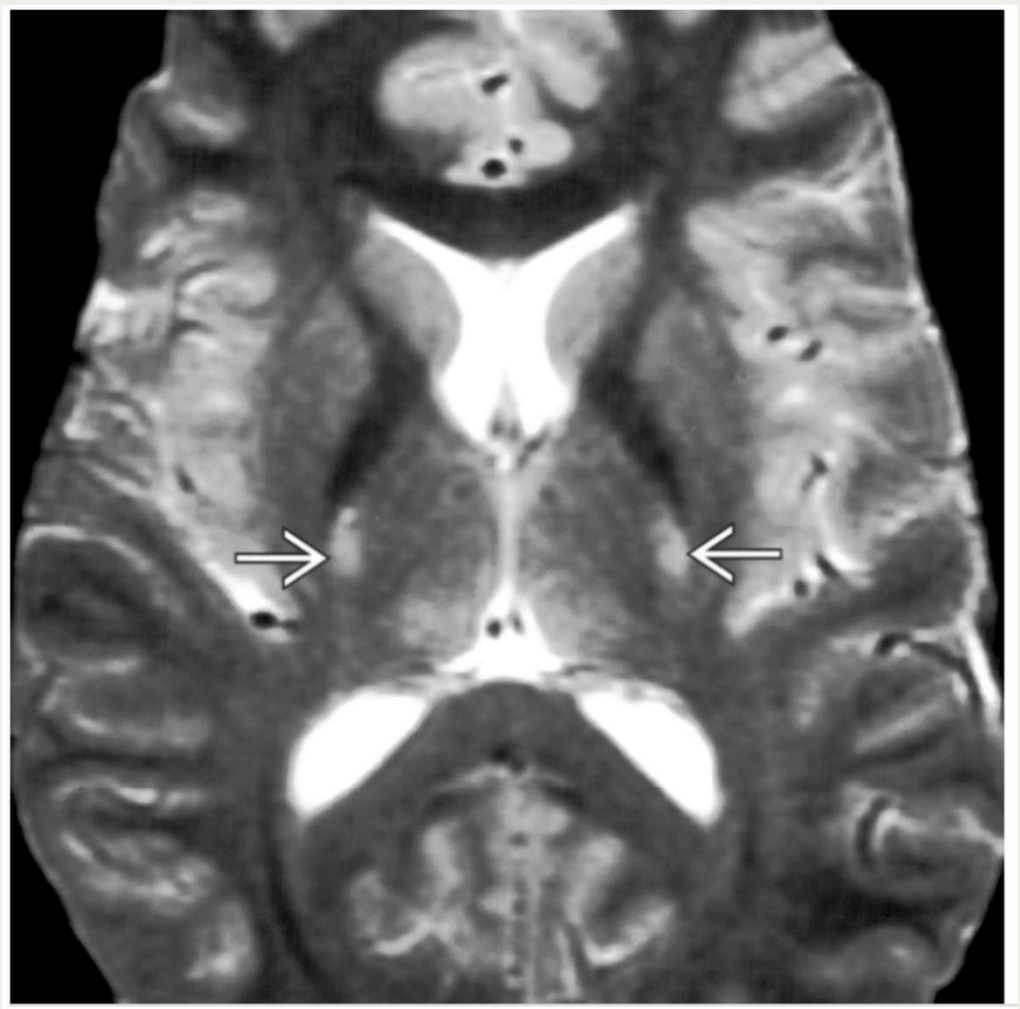
Axial T2WI MR in the same patient shows symmetrical high signal intensity in corona radiata fibers corresponding to corticospinal tracts.



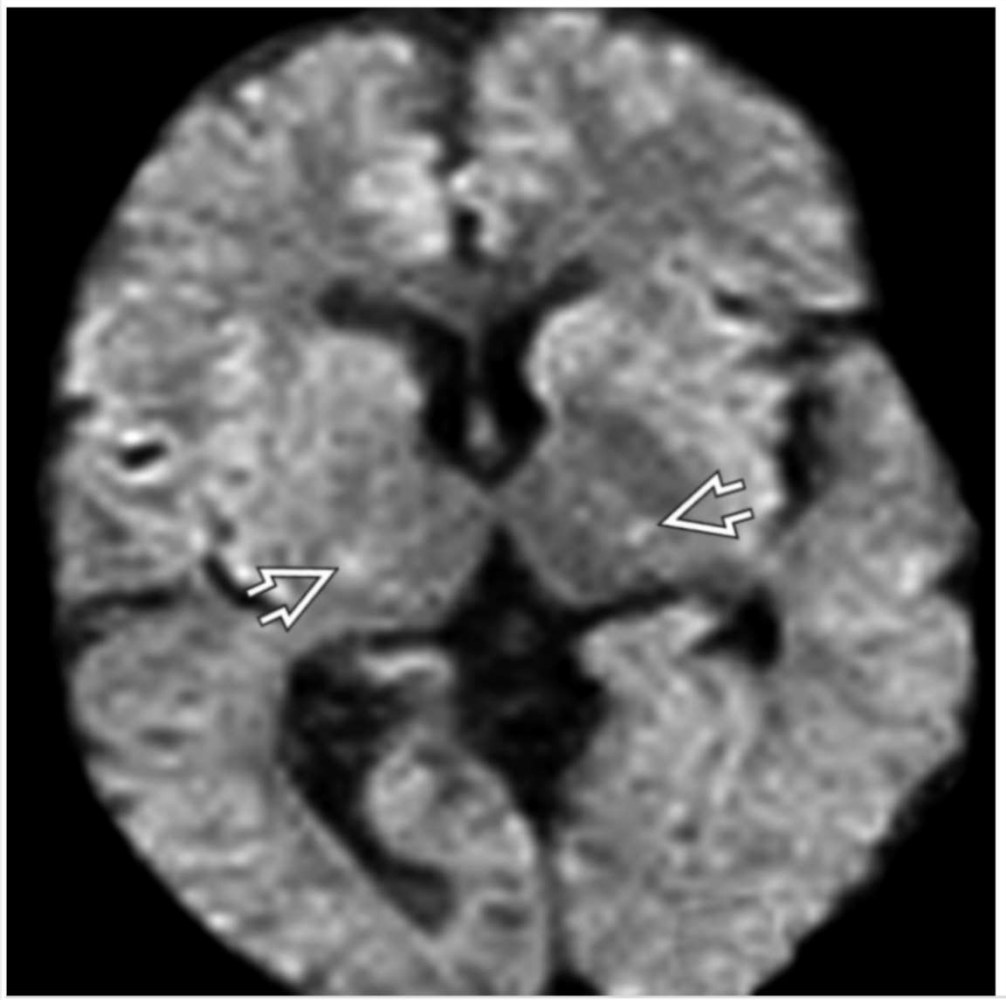
Axial T2WI MR in the same patient demonstrates bilateral low signal intensity in the precentral (motor) cortex.



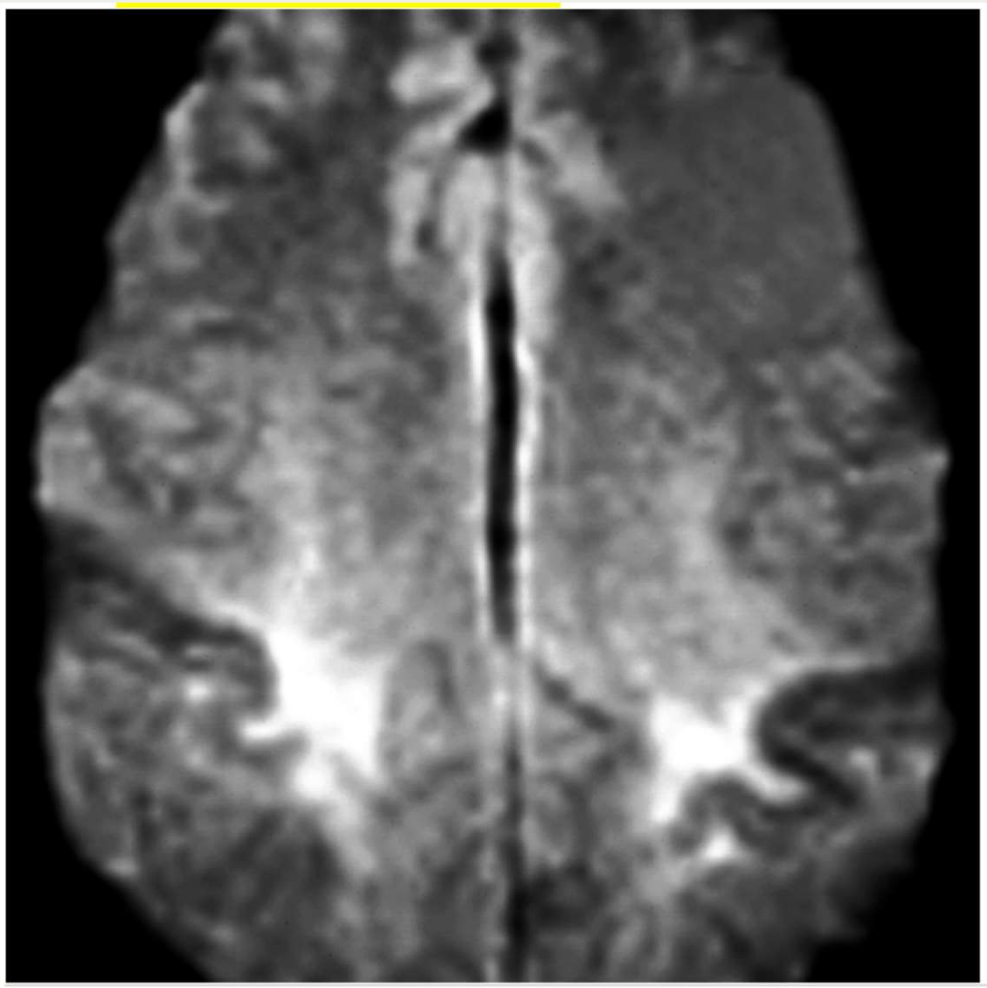
Axial T2WI MR in the same patient with ALS shows symmetric hyperintense corticospinal tracts at the level of the cerebral peduncle.



Axial T2WI MR in a young man with ALS shows symmetric hyperintense corticospinal tracts at the level of the internal capsule.



Axial DWI MR shows small foci of hyperintensity in the posterior limbs of bilateral internal capsules in this ALS patient.



Axial DWI MR shows increased signal involving subcortical white matter of both precentral (motor) gyri, extending caudally into corticospinal tracts (not shown). These findings are typical for ALS.