Occasional essay: upper motor neuron syndrome in amyotrophic lateral sclerosis

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The upper motor neuron syndrome in amyotrophic lateral sclerosis

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**Funding acknowledgements:** MCK receives funding support from the National Health and Medical Research Council of Australia Program Grant (#1132524), Partnership Project (#1153439) and Practitioner Fellowship (#1156093). PNL is supported by funding from: The European Union H2020 Program (Grant No 633413); The MND Association; The Dunhill Trust; The Wellcome Trust. JG is supported by the Dt. Gesellschaft für Muskelkranke (DGM).

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*Word count: 4474*  
*Abstract word count: 164*  
*References: 153*  
*Tables: 1*  
*Illustrations: 1*
Introduction

The diagnosis of amyotrophic lateral sclerosis (ALS) requires recognition of both lower (LMN) and upper motor neuron (UMN) dysfunction. However, classical UMN signs are frequently difficult to identify in ALS. LMN involvement is sensitively detected by electromyography (EMG) but, as yet, there are no generally accepted markers for monitoring UMN abnormalities, the neurobiology of ALS itself, and disease spread through the brain and spinal cord. Full clinical assessment is therefore necessary to exclude other diagnoses and to monitor disease progression. In part, this difficulty regarding detection of UMN involvement in ALS derives from the definition of ‘the UMN syndrome’. Abnormalities of motor control in ALS require reformulation within an expanded concept of the UMN, together with the neuropathological, neuro-imaging and neurophysiological abnormalities in ALS. We review these issues here.

The Lower Motor Neuron

Sir Charles Sherrington (1857-1952) defined the LMN as the anterior horn cell and its motor axon, constituting the final common pathway for reflex action. In 1906 Sherrington, following Hughlings Jackson’s insights, concluded that motor acts were initiated in the brain by sensory input, thus building on activation of this simple reflex pathway, a view further developed by Sir Francis Walshe (1885-1973). Merton et al likened the effect of reflex action to a follow-up length servo, an influential hypothesis, that was subsequently modified as servo assistance to emphasize that stretch reflexes support movement, generated centrally, rather than drive it. Despite these ideas, the UMN syndrome is not well defined.

The Upper Motor Neuron

The clinical criteria (Table 1) used by generations of neurologists to define the ‘corticospinal’ or ‘pyramidal’ syndrome, a term frequently but erroneously regarded as synonymous with ‘UMN syndrome’, rest on surprisingly uncertain pathophysiological underpinnings. The term UMN was introduced by Sir William Gowers (1845-1915) in his Manual of Neurology published before Sherrington’s work. Later, the anatomist, Alf Brodal (1910-1988), emphasized that the UMN consists not just of corticospinal fibres but of all those fibres with motor functions that descend through the pyramids in the lower brainstem on each side. The UMN therefore include crossed and uncrossed corticospinal tracts (CST), corticobulbar,
tectospinal, rubrospinal, vestibulospinal and reticulospinal tracts, as well as various short internuncials and cerebellar connexions.\textsuperscript{15-17} The CSTs constitute only 2-3\% of fibres in the pyramidal UMN pathway.\textsuperscript{18} They provide direct connexions between Betz ‘giant’ cells in primary motor cortex and anterior horn cells in the anterior spinal grey matter and also, through corticobulbar connexions, to neurons in the bulbar motor nuclei. This corticospinal projection consists of large diameter (>10µm), thickly myelinated, monosynaptic, fast-conducting motor efferents. However, most fibres passing caudally through the pyramids are much smaller, <4µm in diameter.\textsuperscript{9,18} The majority of fibres in the medullary pyramids have indirect, polysynaptic projections to spinal interneurons and motoneurons. In addition to the well-known monosynaptic corticomotoneuronal projection, in cat, macaque and humans corticospinal axons have disynaptic projections to upper-limb motoneuron pools through propriospinal neurons located in the C3-C4 levels. This relay allows the corticospinal command to be modulated before it reaches segmental level through a combination of feedback from the moving limb and feedforward inhibition from supraspinal centres. Within these diverse efferent motor projections there are additional descending fibres derived widely from the cerebral cortex, including sensory cortex, that also project to interneurons and primary motor neurons in the anterior horns of the cord, as well as to sensory neurons in the dorsal horn. These descending projections modulate both sensory input to the cord and its motor output.\textsuperscript{19} In summary, the grey matter of the spinal cord is a busy place and much of what goes on there is not under direct voluntary control. This is consistent with the semi-automatic nature of rapid object grasping. As Lemon\textsuperscript{19} summarised: ‘the descending pathways function as part of a large network rather than as separate controllers of the spinal cord’ and ‘the spinal cord functions as part of the brain not as its servant’. The clinical terms “pyramidal syndrome” or “UMN syndrome” conceal a complex motor system.\textsuperscript{9,15}

**The clinician’s corticospinal syndrome**

Hughlings Jackson\textsuperscript{20} made detailed studies of the clinical features of hemiplegia in stroke. He drew attention not only to negative features, such as loss of strength and orienting responses, but also to positive features, such as increased muscular tone, and a brisk knee jerk. The Babinski response was incorporated later (Table 1).\textsuperscript{21-23} In hemiplegia Jackson recognized residual, voluntary limb motor function and characteristic resting limb and body postures. For these and other reasons, especially those related to his observation of the ‘march of focal epilepsy’, he concluded that movements were represented in cerebral cortex and muscles in spinal segments, a view that remains generally accepted.\textsuperscript{24} Modern descriptions of lesions
ascribed to the pyramidal pathway emphasize weakness, loss of dexterity, slowness and poverty of hand movements, brisk tendon reflexes, a spastic increase in muscle tone and the extensor plantar response (Table 1). Spasticity and weakness do not necessarily coexist, and probably relate to dysfunction in different pathways. Denny-Brown and Botterell\textsuperscript{25} found that ablation of Brodmann cortical area 4 in the macaque led to flaccid hemiparesis, followed in a few days by increased tendon jerks and hypertonus of distal limb segments, whereas ablation of Brodmann area 6 caused a more widespread hypertonus resembling the clinician’s ‘extrapyramidal rigidity’.\textsuperscript{25} However, in the macaque, Fulton described spasticity, hemiparesis and apraxia after area 6 ablation.\textsuperscript{26} Much therefore depends on the site and extent of any lesion in the motor system; and also on the ability of researchers to examine primates as fully as human subjects. Walshe\textsuperscript{9} reviewed these and earlier experiments, including early ablation studies in primates,\textsuperscript{27} and studies of electrical stimulation of the cerebral cortex in humans.\textsuperscript{28} He drew the important conclusions that cortical electrical stimulation was likely to be dependent on the characteristics of the stimulation technique, a factor difficult to quantify.\textsuperscript{9}

Tower\textsuperscript{29} found that section of the pyramid at the medullary level in monkey caused a ‘grave and general poverty of movement’ and initial hypotonia. Fine, discrete movements were lost and there was impairment of aim and precision of movement performance, i.e., poverty of movement with loss of dexterity. In the chimpanzee, but not in the monkey, a Babinski reflex could be elicited and there was increased proprioceptive grasping in the upper limb. In searching for methods to alleviate Parkinsonian tremor, Bucy\textsuperscript{30,31} surgically sectioned the human ipsilateral cerebral peduncle. There was less resultant paresis than anticipated and remarkable recovery occurred, but with persistent impairment of fine manipulative finger and hand movement. Electrical stimulation of the uninjured peduncle delineated a medial fronto-pontine bundle, associated with hand and forearm movements, and a more lateral temporo-pontine tract. Mid or upper cervical pyramidotomy, as reported by Lassek et al\textsuperscript{32} for surgical alleviation of tremor, caused paralysis below the site of the lesion that gradually improved, with considerable residual impairment of upper limb movements, weakness of foot dorsiflexion, increased tendon reflexes and a Babinski response.\textsuperscript{32}

The functions of the complex motor pathways at brainstem level were addressed by Lawrence and Kuypers in their now-classic primate experiments.\textsuperscript{33-35} After bilateral pyramidotomy at olivopontine level that interrupted the corticospinal pathway from cortical
area 4, climbing behaviour, as an example of whole body movement, was largely intact, but there was impaired speed and fluency. There was loss of dexterity of hands and digits in retrieving food rewards and isolated actions, such as reaching and grasping, were also severely and permanently affected. Subsequent interruption of the ventromedial descending motor pathway in the medial reticular formation in the floor of the fourth ventricle, consisting of descending fibres from the tectum, the pontine and medullary medial reticular formation and the vestibular complex, caused loss of righting responses, impaired unsupported sitting, walking and climbing and of head, shoulder and trunk movement, but without loss of automatic hand grasping. Lesion of the magnocellular rubrospinal fibres in the lateral medullary brainstem pathway that project to the dorso-lateral zones of the spinal anterior horns, caused loss of ipsilateral hand movements, with a persistent posture of flexion of the arm and extension of the fingers. Bilateral pontine lesions caused similar abnormalities.

Lawrence and Kuypers’ work confirmed that the brain motor system consists of much more than the CST and the primary motor cortex. They concluded that the ventromedial brainstem pathways are the basic system by which the brain controls bodily movement, maintenance of posture, and integration of body-limb movements and locomotion, while the lateral brainstem pathway confers the ability to superimpose independent movements of the extremities, especially the hand, and the corticospinal pathways facilitate further fractionation of movement, especially finger movements. The lateral CSTs project to the intermediate internuncial zone of ventral spinal grey matter, linked to motor neurons innervating muscles of the distal extremities. Corticospinal neurons originating in M1 project directly to these spinal motor neurons, and to the ventromedial intermediate zone controlling trunk and limb-girdle muscles. In addition, some fibres in the CSTs originate in the primary somatosensory cortex and terminate in the spinal dorsal horn.

Single corticomotoneurons and their pyramidal tract axons project to multiple muscles in the primate upper-limb, though usually with a stronger projection to one muscle – stronger and more widespread to extensor muscles than flexors, and stronger distally than proximally. There may be plasticity at the corticomotoneuronal synapse, since connectivity is altered by movement in primates, and segmental interneurons are active during voluntary movement.

As in the cat and the macaque, in human subjects the CST projects to upper cervical propriospinal neurons which then relay some of the corticospinal command to upper limb
motor neurons.\textsuperscript{41,42} This allows updating of the motor command by sensory feedback from the moving limb.\textsuperscript{43} There seem to be no such projections to the intrinsic muscles of the hand.

The UMN deficit in ALS

The UMN features (Table 1) in ALS are not typical of the classic UMN syndrome (Table 1). For example, the plantar responses may be downgoing, even in the presence of other classical UMN features.\textsuperscript{2} UMN lesions cause loss of the local extensor reflexes, such as the plantar reflex response, and also the abdominal and cremasteric reflexes, and disinhibition of the flexion withdrawal response, manifested by activation of extensor hallucis longus and therefore a dorsiflexor (extensor) Babinski toe response,\textsuperscript{44} but this will depend on the force exerted by these opposing reflex systems, which may be disrupted by the motor network disorder in ALS. In ALS there is widespread involvement of the UMN\textsuperscript{2} beyond the archetypal corticospinal lesion familiar from internal capsular infarction.\textsuperscript{16,20} Attribution of components of the motor syndrome in ALS specifically to UMN or LMN dysfunction is difficult since both are usually present. LMN features often predominate and spasticity and increased reflexes may be subtle.\textsuperscript{2} The progressive pattern of LMN weakness and atrophy in ALS suggests relatively orderly spread from a clinical site of origin,\textsuperscript{45} perhaps representing spread by contiguity in spinal segments,\textsuperscript{46,47} but ‘skip lesion’ weakness and atrophy also occur,\textsuperscript{48,49} and a CNS origin for these phenomena has been proposed.\textsuperscript{50}

Kinnier Wilson\textsuperscript{51} taught that flexor muscles are earlier and more severely affected than extensors, although long extensors of the forearm are weakened before long flexors. In the hand the abductor pollicis brevis and first dorsal interrosseous muscles are particularly susceptible but the abductor digitii minimi is relatively spared. This ‘split hand’\textsuperscript{52} has been linked to the dense corticospinal innervation of the more susceptible muscles\textsuperscript{53} associated with their importance in thumb movement and grasping,\textsuperscript{50} but this pattern of wasting is inconstant and other, perhaps related, explanations are possible.\textsuperscript{54} The motor syndrome in ALS includes abnormalities of stance and balance, and of foot placement, sometimes with features consistent with loss of orienting reflexes.\textsuperscript{55} Hand and finger movement is often markedly affected, with loss of dexterity and slowness of movement, sometimes described as clumsiness, in addition to objective weakness of grasp and other hand and finger movements. The gait is also clumsy and unreactive to barriers, as in managing ambulation over a rough surface. When there is bulbar involvement the normal precise coordination of respiratory pattern, voice, speech, swallowing, saliva management, and facial movement is impaired.
causing degradation and coarseness of all these functions. These deficits result from
degeneration of small-fibre propriospinal rather than corticospinal motor pathways and their
central network connections, as shown by the Lawrence and Kuypers experiments described
above.

**Higher-order functional motor deficits in ALS**

Loss of dexterity is a well-recognised feature of the “UMN syndrome” in stroke. When the
corticospinal tract is damaged, recovery of the function of intrinsic muscles of the hand is
less reliant on oligosynaptic corticospinal and other descending inputs, because they are the
only upper-limb muscles to receive an exclusively monosynaptic (and lateralised)
corticospinal input. In his textbook Kinnier Wilson commented on prominent
‘awkwardness of fine finger movements’ in the early stages of ALS, despite only slight
weakness and the absence of spasticity. This forgotten observation suggests a higher-order
motor defect, or apraxia, associated with frontotemporal cortical atrophy and the associated
tract degeneration that characterize the CNS disorder in ALS and ALS-FTLD. Higher-order
motor deficits are particularly evident in behavioural variant FTLD, manifest by motor
slowness and loss of intuitive, complex patterns of voluntary movement, and dominated by a
prominent frontal executive syndrome with frontal and prefrontal cortical atrophy, with or
without an associated ALS syndrome.

The term apraxia has not been applied to the motor disorder in ALS perhaps because this
extends the concept of apraxia beyond its classical definition as a higher-order motor disorder
in the absence of focal neurological signs, especially weakness or sensory loss. However,
in modern usage, apraxia, due to loss of specialised cortical function from focal lesion or
degeneration, has been termed ‘hodological apraxia’, and disconnexion syndromes due to
fibre tract degeneration, ‘topological apraxia’. Cortical and pathway lesions may induce
increased or decreased excitability in the damaged motor system. Recognition of higher-
level motor disturbances in ALS extends understanding of the UMN or central motor
dysfunction. ALS patients require marked effort to achieve adequate velocity and precision of
movement, but retain ability to visualize and describe motor components necessary to
perform fine graduated movements. Thus, the core features of ideomotor apraxia are absent,
in ALS although they may be recognisable in ALS-FTLD. In ALS, the cortical disorder
and secondary motor tract degeneration cause disconnexion of the cerebral motor systems
from the spinal cord motor systems, including propriospinal motor connections and
proprioceptive control mechanisms. Disruption and slowness of movement in ALS results both from degeneration in descending motor pathways and loss of control mechanisms; for example, connexions to basal ganglia and cerebellum that normally fine tune the motor drive.

Neuropathology of the UMN in ALS

Pathological studies of the CNS in ALS are inevitably limited to end-stage disease. The first descriptions of cellular pathology in the motor cortex and subcortical motor pathways derive from Marie who, with Charcot, described ‘atrophy of the large pyramidal cells of the cortex’, loss of these cells, and ‘numerous granular bodies’ in the subcortical white matter, interpreted as degenerating corticofugal fibres. Degeneration of corticofugal fibres was traced through the internal capsule into the cerebral peduncles, the medullary pyramids and spinal cord, but was not seen at a higher level, in contrast to the pattern of degeneration following vascular lesions of the motor cortex in which the process progressed caudally - a ‘dying forward’ process. Marie therefore dismissed the notion that in ALS degeneration of the CST proceeds caudally from the motor cortex to the spinal cord, in parallel with loss of spinal motor neurons: “Unfortunately, gentlemen, this seductive theory very imperfectly explains the morbid process which produces amyotrophic lateral sclerosis and serious objections may be made to its adoption”. This puzzle remains unresolved but is consistent with emerging concepts of ALS as a network connectivity disorder.

There is variable loss of pyramidal neurons in ALS, particularly Betz cells, in the primary motor cortex and surrounding areas, but cerebral pathology is not solely restricted to the primary motor cortex. In ALS-FTLD syndromes there is marked frontal atrophy; with neuronal loss in layers 2, 3 and 5, ‘status spongiosus’, astrogliosis, and microglial proliferation as co-indicators of widespread pathology. At autopsy abnormalities in ALS are widespread in central motor pathways. Loss of pyramidal neurons in layers 4 and 5 of the primary motor cortex, and of cortical peptidergic and GABAergic interneurons is controversial, but loss of pyramidal cells and interneurons extends to cortical areas 4, 9 and 24. Loss of cortical pyramidal neurons and interneurons in distant, indirectly connected cortical areas is consistent with the notion that ALS and FTLD are related anterior brain degenerations. Selective susceptibility of long axons, as a concept, has been superseded by the notion of vulnerability of functionally related neuronal and glial networks, associated with TDP43 deposits in remaining neurons. It is difficult to correlate clinical phenotype with motor or frontal cortical or CST pathology in ALS. Indeed, in progressive muscular
atrophy (PMA) despite little or no clinical evidence of UMN involvement there is almost universal pathological evidence of CST degeneration,\(^{74,75}\) perhaps clinically undetectable due to the extent of LMN loss and muscle atrophy.

Overall, therefore, the pathological evidence points towards a process of axonal degeneration. Occasionally MRI reveals striking signal change in the cerebral CSTs\(^{76}\) but whether or not this represents Wallerian degeneration, a progressive anterograde degeneration of axons in reaction to injury, is unclear.\(^{77,78}\) However, blocking the molecular pathways that contribute to Wallerian degeneration does not modulate neurodegeneration in mouse ALS models.\(^{79}\)

Neuronal cell bodies and axons in CNS motor pathways seem to be involved together..

Intracellular inclusions containing ubiquitin, p62, and abnormal TDP-43 are far less marked in cortical motor neurons than in somatic motor neurons of the brain stem and spinal cord, or in neurons in layers 2, 3 and 5 in the prefrontal and temporal regions in FTLD and ALS-FTLD. Altered TDP-43 probably drives degeneration in the CST. Abnormalities in Betz cells and pyramidal cells of the primary motor cortex in sporadic and familial ALS, and in ALS-FTLD, include fragmentation, vacuolation, and atrophy of apical dendrites, loss of spines, apical dendrite retraction and loss of postsynaptic densities.\(^{80-83}\) Studies in animal models suggest that dendritic pathology is an early, indeed pre-symptomatic, feature of ALS\(^{84-86}\) and that TDP-43 cytoplasmic mislocalisation is associated with reduction in dendritic spine density.\(^{86}\) How far these observations mirror the evolution of pathology in human ALS is uncertain.\(^{87}\) In summary, there is incomplete understanding of the dynamics of UMN degeneration in ALS.\(^{65}\) Genetic heterogeneity, and the wide variation in the distribution and burden of UMN pathology across the ALS and ALS-FTLD syndromes, suggests marked variability in the underlying dynamic processes, even in clinically similar ALS syndromes.\(^{88}\)

**Structural biochemistry of the UMN in ALS**

Neurofilaments (NFs) are components of the neuronal cytoskeleton, classified by molecular weight into light chain (NfL), heavy chain (NfH) and intermediate chain. Raised CSF and blood levels have been demonstrated in many CNS diseases, correlated with the clinical intensity and presumably reflecting the rate of neuronal and axonal loss.\(^{89}\) In the earliest reports of raised CSF NF levels seen in ALS, it was noted that levels were highest in those with UMN signs.\(^{90,91}\) This was replicated in larger patient series, in which a strong relationship to rate of increasing disability was confirmed.\(^{92}\) The assumption that high CSF
levels in ALS reflect CST damage was tested using paired diffusion tensor imaging measures, but the results showed limited or no apparent association. Additional CSF and blood-based studies have reported only weak distinction between NF levels and clinical UMN versus LMN involvement in ALS.

**Imaging in ALS: widespread UMN abnormalities**

Macroscopic post mortem cerebral atrophy is strikingly limited in ALS. Localized, ‘knife-edge’ atrophic pre-central gyri are seen in slowly progressive cases, especially in Primary Lateral Sclerosis, a syndrome in which degeneration is clinically limited to the UMN. Automated volumetric MRI studies in ALS may detect diffuse frontal cerebral atrophy, especially associated with cognitive impairment but there is currently only limited evidence supporting somatotopic motor cortical atrophy in relation to regional motor disability. In some patients there is hyperintensity in the CSTs in T2-weighted MRI, but with weak clinical correlation. However, T2-based MRI signal analysis, using diffusion tensor imaging (DTI), has confirmed consistent loss of CST integrity more consistently related to classic clinical UMN involvement. Linkage of primary motor cortical atrophy and clinical UMN signs is strengthened by MR spectroscopy, using reduced N-acetylaspartate levels as a surrogate marker for neuronal loss, both in region-of-interest and whole-brain studies. Interhemispheric motor cortical fibres in the central corpus callosum (Fig 1) are consistently involved in ALS, especially in PLS. DTI changes correlate with clinical and transcortical magnetic stimulation studies of UMN involvement and Wallerian degeneration with microglial infiltration has been suggested as correlates of these white matter tract MRI changes.

White matter tract damage in ALS (Fig 1) is invariably bilateral in DTI studies and extends far beyond the pyramidal tracts and the corpus callosum, even in patients studied soon after the onset of focally restricted symptoms. Structural studies focused beyond the cortical grey matter in ALS have shown associated changes in basal ganglia, particularly in the thalami - points of integration with widespread frontotemporal cortical involvement in the course of the disease. MRI has confirmed the neuropathological finding that in progressive muscular atrophy (PMA) there is typically also sub-clinical degeneration of the pyramidal pathway.
Neuroimaging markers and disability in ALS are poorly correlated, reflecting dependence of the ALS Functional Rating Scale on LMN loss. Functional brain imaging with positron emission tomography (PET), using radiotracers sensitive to glucose metabolism and blood flow has also demonstrated brain changes beyond primary motor regions. Blood flow PET during performance of a focused upper limb task revealed cortical activation extending to facial areas of the motor cortex, implying an alteration in local circuit neurophysiology, whether compensatory or a primary pathological process. Subsequent ligand PET studies using Flumazenil as a marker of GABAergic inhibitory receptors showed loss of binding in motor and premotor regions in ALS, but with relative preservation in familial slowly-progressive ALS. Combined DTI and functional MRI studies provide limited support for a more direct role of inhibitory interneuron loss in the pathogenesis of ALS, rather than a solely compensatory process and MR spectroscopy has provided limited evidence for reduced GABA-ergic influence within the primary motor cortex.

Functional MRI based on regional patterns of synchronously fluctuating blood oxygenation level-dependent (BOLD) signal in the task-free, so-called resting state, has revealed a network-based dysfunction underlying neurodegenerative disorders more broadly, but also to ALS. Resting state network abnormalities, in the form of increased functional connectivity, are detectable in asymptomatic carriers of penetrant ALS-causing genetic variants. Further, the unique temporal sensitivity of magnetoencephalography in demonstrating differences in beta-band cortical oscillations associated with the preparation, execution and recovery from motor activity promises to be potentially powerful for studies of corticomuscular coherence in analysing broader motor system ‘connectome’ dysfunction in ALS.

Neurophysiological studies of the UMN in ALS

Early studies used transcranial electrical stimulation of the motor cortex. This induced depolarization of large pyramidal neurons, and showed absent or delayed cortical responses, confirming that the fast conducting UMN tract was damaged in this disorder. The central conduction time was found to be more frequently delayed in patients with UMN signs and this test was more sensitive than clinical assessment in the identification of UMN dysfunction. Transcranial magnetic stimulation (TMS), which superseded electrical brain stimulation, induces an intracortical current causing a transmembrane ionic flow that induces preferential transsynaptic excitation of pyramidal cells. Motor cortical dysfunction,
related to clinical findings, is detectable in ~70% of ALS patients,\textsuperscript{134} and in ~30% of those with pure LMN presentations.\textsuperscript{134,135} In addition, in early ALS the cortical motor threshold is reduced in strong muscles, in particular in those with fasciculations.\textsuperscript{134-138} Short interval intracortical inhibition (SICI), 1-4ms, measured using a paired stimulus technique is mediated by GABA-ergic (GABA-A) interneuronal circuits, and is reduced in ALS.\textsuperscript{139,140} An automated cortical threshold tracking technique, recording decreased motor amplitude in the target muscle\textsuperscript{141} has shown that this is a consistent early marker of ALS, and that it precedes clinical onset in SOD1 familial ALS. Furthermore, this abnormality is partially normalized by riluzole.\textsuperscript{142} Peri-stimulus time histogram studies in early affected patients showed increased magnitude of EPSPs.\textsuperscript{143} Fasciculations, a typical marker of LMN dysfunction in ALS, can sometimes be evoked by TMS,\textsuperscript{144} probably representing LMN hyperexcitability.

Spasticity, a feature of the classical UMN syndrome, is a sign of alpha-corticomotoneuronal hyperexcitability.\textsuperscript{39} This membrane change is associated with stable membrane potentials (plateau potentials), that resist changes in response to peripheral inputs,\textsuperscript{145} shown by analyzing the variability of the LMN firing rate in ALS and PLS.\textsuperscript{146} The cortical silent period (CSP), mainly representing cortical inhibition,\textsuperscript{147} is a period of EMG silence during muscle contraction following a motor response evoked by TMS. It tends to be shorter in ALS, especially early in disease progression.\textsuperscript{148} The H-reflex, mirroring the monosynaptic tendon-reflex, is abnormal consistent with clinical signs of UMN involvement, especially in analyses of the slope angle of its earliest rising phase.\textsuperscript{149} These changes are consistent with coupled UMN-LMN hyperexcitability. However, adapted interneuronal responses in the spinal cord resulting from reduced corticospinal input, leading to increased compensatory alpha-motoneuron hyperexcitability are also a possible mechanism.\textsuperscript{150} Hyperexcitability may be an early feature of neuronal degeneration but, also, a transitory adaptive process to compensate for neuronal loss, although the latter seems less likely.\textsuperscript{151,152} Current neurophysiological methods do not address function in most of the ancillary UMN pathways, as reviewed above, that have a critical role in the disease process. In addition, the role of spinal cord UMN pathways, an integral component of the CNS, is not well defined.

**Conclusions**

ALS is a disorder characterised by anterior brain neurodegeneration, that seems to result from interactions between genetic and potential environmental risk factors, with striking clinical variability.\textsuperscript{88} Recognition of the UMN abnormality in ALS has always been difficult,
despite its importance for robust diagnosis.\textsuperscript{1,3,4} This reflects diagnostic emphasis on the classical clinical signs of internal capsular lesions as the epitome of the UMN syndrome. However, in ALS, frontal brain degeneration is widespread, with complex secondary efferent and commissural tract degenerations diffusely involving the brain motor network and its related connections. Involvement of other brain structures, including thalamic\textsuperscript{123} and cerebellar changes,\textsuperscript{153} and the anterior horns in the spinal cord,\textsuperscript{2} and frontal cognitive abnormalities, is consistent with this concept of anterior brain degeneration. In ALS and ALS-FTLD classical UMN features, as seen in focal brain lesions, are overwhelmed by anterior horn cell and interneuronal degeneration in the spinal cord,\textsuperscript{2} and by higher-order functional motor deficits. The latter have been underestimated by ALS clinicians. Expansion of the concept of the UMN deficit in the ALS syndrome, including structural and functional brain imaging and neurophysiological assessment of cortical and deep white matter motor systems will facilitate understanding of the functional deficits. Given the pathophysiological complexity of the UMN syndrome it is not surprising that the full clinical syndrome is often not present in ALS, underlying the need for surrogate markers of UMN dysfunction. A wider concept of the UMN syndrome in ALS is required.
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Table 1: Classical clinical features of upper and lower motor neuron syndromes

Note that these traditional criteria do not include any higher-order functional tests in the case of UMN disorders, which could distinguish fronto-temporal cerebral dysfunction from limited lesions in the CSTs in the brainstem or spinal cord. Internal capsular lesions frequently involve non-corticospinal descending pathways, in addition to the corticospinal pathways themselves.

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<th>Clinical sign</th>
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<tr>
<td>weakness</td>
<td>“pyramidal” distribution; i.e. hip flexor and foot dorsiflexor predominant</td>
<td>focal or multifocal, often in peripheral nerve or root distribution</td>
</tr>
<tr>
<td>loss of distal dexterity</td>
<td>present</td>
<td>absent if no sensory loss</td>
</tr>
<tr>
<td>slowness and simplification of movement</td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td>poor balance responses</td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td>fatigue</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>muscular atrophy</td>
<td>slight or absent</td>
<td>prominent in weak muscles</td>
</tr>
<tr>
<td>muscular tone</td>
<td>increased with spasticity</td>
<td>reduced in weak muscles</td>
</tr>
<tr>
<td>deep tendon and superficial reflexes</td>
<td>tendon reflexes increased Supercillex reflexes diminished</td>
<td>tendon reflexes reduced or absent superficial reflexes normal or reduced</td>
</tr>
<tr>
<td>Babinski response (and related responses)</td>
<td>present</td>
<td>absent</td>
</tr>
<tr>
<td>fasciculation</td>
<td>absent</td>
<td>present</td>
</tr>
</tbody>
</table>
**Fig 1: Diffusion Tensor Imaging (DTI) in ALS**

DTI is a non-invasive, in vivo application of MRI that is sensitive to a reduction in unidirectional water movement associated with the loss of large white matter tract integrity arising through a variety of brain pathologies. In ALS, there is a consistent reduction in a quantifiable metric known as fractional anisotropy, that is most consistently spatially localised to the caudal CST and interhemispheric motor fibres of the corpus callosum (marked on the images here in yellow and orange over the background DTI white matter tract skeleton, shown in green).