Occasional essay: Upper motor neuron syndrome in amyotrophic lateral sclerosis

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INTRODUCTION

The diagnosis of amyotrophic lateral sclerosis (ALS) requires recognition of both lower motor neuron (LMN) and upper motor neuron (UMN) dysfunction.[1] However, classical UMN signs are frequently difficult to identify in ALS.[2] LMN involvement is sensitively detected by electromyography (EMG),[3] but, as yet, there are no generally accepted markers for monitoring UMN abnormalities,[4] the neurobiology of ALS itself and disease spread through the brain and the spinal cord.[5] 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, neuroimaging and neurophysiological abnormalities in ALS. We review these issues here.

THE LMN

Sir Charles Sherrington (1857–1952) defined the LMN[6 7] as the anterior horn cell and its motor axon, constituting the final common pathway for reflex action.[8] In 1906, Sherrington,[7] 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).[9] Merton[10] likened the effect of reflex action to a follow-up length servo, an influential hypothesis that was subsequently modified as servo assistance to emphasise that stretch reflexes support movement, generated centrally, rather than drive it.[11 12] Despite these ideas, the UMN syndrome is not well defined.[7 13–15]

THE UMN

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,[13] published before Sherrington's work.[14] Later, the anatomist, Alf Brodal (1910–1988), emphasised that the UMN[16] 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 UMNs therefore include crossed and uncrossed corticospinal tracts (CSTs) and corticobulbar, tectospinal, rubrospinal, vestibulospinal and reticulospinal tracts, as well as various short internuncials and cerebellar connections.[15–17] The CSTs constitute only 2%–3% of fibres in the pyramidal UMN pathway.[18] They provide direct connections between Betz 'giant' cells in the primary motor cortex and anterior horn cells in the anterior spinal grey matter and, also, through corticobulbar connections to neurons in the bulbar motor nuclei. This corticospinal projection consists of large-diameter (>10 µm), thickly myelinated, monosynaptic, fast-conducting motor efferents. However, most fibres passing caudally through the

Table 1 Classical clinical features of UMN and LMN syndromes

Clinical sign	UMN syndrome	LMN syndrome
Weakness	'Pyramidal' distribution, that is, hip flexor and foot dorsiflexor predominant	Focal or multifocal, often in peripheral nerve or root distribution
Loss of distal dexterity	Present	Absent if no sensory loss
Slowness and simplification of movement	Present	Absent
Poor balance responses	Present	Absent
Fatigue	Present	Present
Muscular atrophy	Slight or absent	Prominent in weak muscles
Muscular tone	Increased with spasticity	Reduced in weak muscles
Deep tendon and superficial reflexes	Tendon reflexes increased or superficial reflexes diminished	Tendon reflexes reduced or absent superficial reflexes normal or reduced
Babinski response (and related responses)	Present	Absent
Fasciculation	Absent	Present

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

pyramids are much smaller, <4 µm in diameter.[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 cats, macaques 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 the 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 the 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.[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 semiautomatic nature of rapid object grasping. As Lemon[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.[9 15]

THE CLINICIAN'S CORTICOSPINAL SYNDROME

Hughlings Jackson[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).[21–23] In hemiplegia, Jackson recognised 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 the cerebral cortex and muscles in spinal segments, a view that remains generally accepted.[24] Modern descriptions of lesions ascribed to the pyramidal pathway emphasise 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[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 hypertonic distal limb segments, whereas ablation of Brodmann area 6 caused a more widespread hypertonus resembling the clinician's 'extrapyramidal rigidity'.[25] However, in the macaque, Fulton described spasticity, hemiparesis and apraxia after area 6 ablation.[26] Much therefore depends on the site and the extent of any lesion in the motor system, and also on the ability of researchers to examine primates as fully as human subjects. Walshe[9] reviewed these and earlier experiments, including early ablation studies in primates,[27] and studies of electrical stimulation of the cerebral cortex in humans.[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.[9]

Tower[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, that is, 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[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 movements. Electrical stimulation of the uninjured peduncle delineated a medial frontopontine bundle, associated with hand and forearm movements, and a more lateral temporopontine tract. Mid or upper cervical pyramidotomy, as reported by Lassek *et al*[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.[32]

The functions of the complex motor pathways at the brainstem level were addressed by Lawrence and Kuypers in their now-classic primate experiments.[33–35] After bilateral pyramidotomy at the 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. Lesions of the magnocellular rubrospinal fibres in the lateral medullary brainstem pathway that project to the dorsolateral 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.[33 34] 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 the 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.[36] There may be plasticity at the corticomotoneuronal synapse, since connectivity is altered by movement in primates,[37] and segmental interneurons are active during voluntary movement.[38]

As in the cat[39] and the macaque,[40] in human subjects the CST projects to upper cervical propriospinal neurons, which then relay some of the corticospinal command to upper-limb motor neurons.[41 42] This allows updating of the motor command by sensory feedback from the moving limb.[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.[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,[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 In ALS, there is widespread involvement of the UMN[2] beyond the archetypal corticospinal lesion familiar from internal capsular infarction.[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.[2] The progressive pattern of LMN weakness and atrophy in ALS suggests a relatively orderly spread from a clinical site of origin,[45] perhaps representing spread by contiguity in spinal segments,[46 47] but 'skip lesion' weakness and atrophy also occur,[48 49] and a central nervous system (CNS) origin for these phenomena has been proposed.[50]

Kinnier Wilson[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 the first dorsal interroseous muscles are particularly susceptible, but the abductor digiti minimi is relatively spared. This 'split hand'[52] has been linked to the dense corticospinal innervation of the more susceptible muscles[53] associated with their importance in thumb movement and grasping,[50] but this pattern of wasting is inconstant and other, perhaps related, explanations are possible.[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.[55] Hand and finger movements are 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 previously.

HIGHER-ORDER FUNCTIONAL MOTOR DEFICITS IN ALS

Loss of dexterity is a well-recognised feature of the UMN syndrome in stroke.[56] When the CST 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.[42] 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'.[51] This forgotten observation suggests a higher-order motor defect, or apraxia, associated with frontotemporal cortical atrophy and the associated tract degeneration that characterise the CNS disorder in ALS and ALS-FTLD (frontotemporal lobar dementia). Higher-order motor deficits are particularly evident in behavioural variant FTLD, manifested 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.[57 58] However, in modern usage, apraxia due to loss of specialised cortical function from focal lesion or degeneration has been termed 'hodological apraxia', and disconnection syndrome due to fibre tract degeneration has been termed 'topological apraxia'.[59] Cortical and pathway lesions may induce increased or decreased excitability in the damaged motor system.[59] Recognition of higher-level motor disturbances in ALS extends understanding of the UMN or central motor dysfunction. Patients with ALS require marked effort to achieve adequate velocity and precision of movement, but retain the ability to imagine and describe motor components necessary to perform fine graduated movements. Thus, the core features of ideomotor apraxia are absent in ALS,[57 58] although they may be recognisable in ALS-FTLD. In ALS, the cortical disorder and secondary motor tract degeneration cause disconnection 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 result both from degeneration in descending motor pathways and loss of control mechanisms, for example, connections 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.[60 61] Degeneration of corticofugal fibres was traced through the internal capsule into the cerebral peduncles, the medullary pyramids and the spinal cord but was not seen at a higher level,[62–64] in contrast to the pattern of degeneration following vascular lesions of the motor cortex in which the process progressed caudally, a 'dying forward' process.[60] 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 ALS and serious objections may be made to its adoption'.[60] This puzzle remains unresolved'[65] 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,[63 64 66–69] but cerebral pathology is not solely restricted to

the primary motor cortex.[7 64] In ALS-FTLD syndromes, there is marked frontal atrophy; with neuronal loss in layers 2, 3 and 5, 'status spongiosus', astrogliosis and microglial proliferations as coindicators 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 (gamma-amino-butyric acid) interneurons[70 71] is controversial,[72] 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,[73] 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 phenotypes with motor or frontal cortical or CST pathology in ALS.[63–66] 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 a 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.[77 782] 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 brainstem 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, 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 presymptomatic feature of ALS[84–86] and that TDP-43 cytoplasmic mislocalisation is associated with a reduction in dendritic spine density.[862] 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 suggest 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, heavy chain and intermediate chain. Raised cerebrospinal fluid (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 (DTI) measures, but the results showed limited[5] or no apparent association.[93] Additional CSF and blood-based studies have reported only a weak distinction between NF levels and clinical UMN versus LMN involvement in ALS.[94 95]

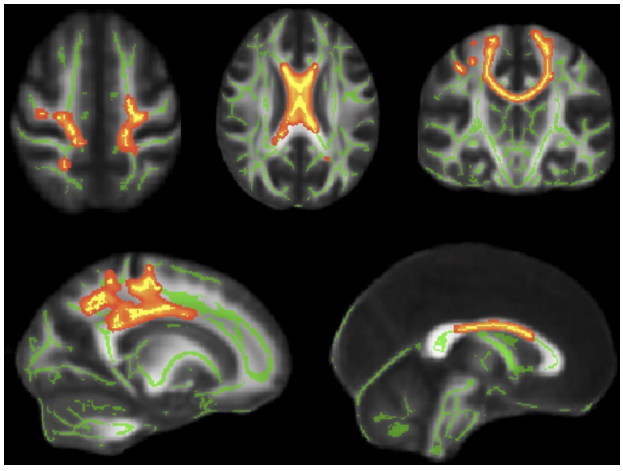

Figure 1 DTI in ALS. DTI is a non-invasive, in vivo application of MRI that is sensitive to a reduction in unidirectional water movement associated with the loss of large white matter tract integrity arising through a variety of brain pathologies. In ALS, there is a consistent reduction in a quantifiable metric known as fractional anisotropy, which is most consistently spatially localised to the caudal corticospinal tract 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). ALS, amyotrophic lateral sclerosis; DTI, diffusion tensor imaging.

IMAGING IN ALS: WIDESPREAD UMN ABNORMALITIES

Macroscopic postmortem cerebral atrophy is strikingly limited in ALS. Localised, 'knife-edge', atrophic, precentral gyri are seen in slowly progressive cases, especially in primary lateral sclerosis (PLS), a syndrome in which degeneration is clinically limited to the UMN.[96] Automated volumetric MRI studies in ALS may detect diffuse frontal cerebral atrophy, especially associated with cognitive impairment,[97–99] but there is currently only limited evidence supporting somatotopic motor cortical atrophy in relation to regional motor disability.[99 100] In some patients, there is hyperintensity in the CSTs in T2-weighted MRI,[101] but with weak clinical correlation.[102] However, T2-based MRI signal analysis, using DTI, has confirmed consistent loss of CST integrity more consistently related to classic clinical UMN involvement.[103] Linkage of primary motor cortical atrophy and clinical UMN signs is strengthened by magnetic resonance (MR) spectroscopy, using reduced N-acetylaspartate levels as a surrogate marker for neuronal loss, both in region-of-interest[104] and whole-brain studies.[105] Interhemispheric motor cortical fibres in the central corpus callosum (figure 1) are consistently involved in ALS,[106–108] especially in PLS.[109 110] DTI changes correlate with clinical and transcortical magnetic stimulation studies of UMN involvement,[107 109 111] and Wallerian degeneration with microglial infiltration has been suggested as a correlate of these white matter tract MRI changes.[112 113]

White matter tract damage in ALS (figure 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.[114] Structural studies focused beyond the cortical grey matter in ALS have shown

associated changes in basal ganglia,[99] particularly in the thalami, points of integration with widespread frontotemporal cortical involvement in the course of the disease.[115] MRI has confirmed the neuropathological finding that in PMA there is typically also subclinical degeneration of the pyramidal pathway.[74 75]

Neuroimaging markers and disability in ALS are poorly correlated, reflecting dependence of the ALS Functional Rating Scale on LMN loss.[116] 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.[117 118] 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.[119] 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.[120] 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,[121] and MR spectroscopy has provided limited evidence for reduced GABA-ergic (GABA-A) influence within the primary motor cortex.[122]

Functional MRI based on regional patterns of synchronously fluctuating blood oxygenation level-dependent signal in the task-free, so-called resting state has revealed a network-based dysfunction underlying neurodegenerative disorders more broadly,[123] but also to ALS.[124] Resting-state network abnormalities, in the form of increased functional connectivity, are detectable in asymptomatic carriers of penetrant ALS-causing genetic variants.[125] 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[126] promises to be potentially powerful for studies of corticomuscular coherence in analysing broader motor system 'connectome' dysfunction in ALS.[127]

NEUROPHYSIOLOGICAL STUDIES OF THE UMN IN ALS

Early studies used transcranial electrical stimulation of the motor cortex.[128] This induced depolarisation of large pyramidal neurons and showed absent or delayed cortical responses, confirming that the fast-conducting UMN tract was damaged in this disorder.[129–131] The central conduction time was found to be more frequently delayed in patients with UMN signs,[129] and this test was more sensitive than clinical assessment in the identification of UMN dysfunction.[129–131] Transcranial magnetic stimulation[132] (TMS), which superseded electrical brain stimulation, induces an intracortical current causing a transmembrane ionic flow that induces preferential trans-synaptic excitation of pyramidal cells.[133] Motor cortical dysfunction, related to clinical findings, is detectable in ~70% of patients with ALS,[134] and in ~30% of those with pure LMN presentations.[134 135] In addition, in early ALS the cortical motor threshold is reduced in strong muscles, in particular in those with fasciculations.[134–138] Short-interval intracortical inhibition (1–4 ms), measured using a paired stimulus technique, is mediated by GABA-A interneuronal circuits and is reduced in ALS.[139 140] An automated cortical threshold tracking technique, recording decreased motor amplitude in the target muscle,[141] has shown that this is a consistent early marker of ALS and that it precedes clinical onset in superoxide dysmutase (SOD1) familial ALS. Furthermore, this abnormality is partially normalised by riluzole.[142] Peristimulus time histogram studies in early affected patients showed increased magnitude of excitatory postsynaptic potentials (EPSPs).[143] Fasciculations, a typical marker of LMN dysfunction in ALS, can sometimes be evoked by TMS,[144] probably representing LMN hyperexcitability.

Spasticity, a feature of the classical UMN syndrome, is a sign of alpha-corticomotoneuronal hyperexcitability.[39] This membrane change is associated with stable membrane potentials (plateau potentials) that resist changes in response to peripheral inputs,[145] shown by analysing the variability of the LMN firing rate in ALS and PLS.[146] The cortical silent period, mainly representing cortical inhibition,[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.[148] The H-reflex, mirroring the monosynaptic tendon reflex, is abnormally consistent with clinical signs of UMN involvement, especially in analyses of the slope angle of its earliest rising phase.[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.[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.[127 151] Current neurophysiological methods do not address function in most of the ancillary UMN pathways, as reviewed previously, 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.[88] Recognition of the UMN abnormality in ALS has always been difficult despite its importance for robust diagnosis.[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[123] and cerebellar changes,[152] the anterior horns in the spinal cord[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[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 must be developed.

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REFERENCES

1 Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/ Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial 'Clinical limits of amyotrophic lateral sclerosis' workshop contributors. *J Neurol Sci* 1994;124 Suppl:96–107.
2 Swash M. Why are upper motor neuron signs difficult to elicit in amyotrophic lateral sclerosis? *J Neurol Neurosurg Psychiatry* 2012;83:659–62.
3 Carvalho MD, Swash M. Awaji diagnostic algorithm increases sensitivity of El Escorial criteria for ALS diagnosis. *Amyotroph Lateral Scler* 2009;10:53–7.
4 de Carvalho M, Dengler R, Eisen A, *et al*. Electrodiagnostic criteria for diagnosis of ALS. *Clin Neurophysiol* 2008;119:497–503.
5 Menke RAL, Gray E, Lu C-H, *et al*. CSF neurofilament light chain reflects corticospinal tract degeneration in ALS. *Ann Clin Transl Neurol* 2015;2:748–55.
6 Liddell EGT, Sherrington CS. Recruitment and some other features of reflex inhibition. *Proc Roy Soc* 1925;97B:488–518.
7 Sherrington CS. *Integrative action of the nervous system*. New Haven: Yale University Press, 1906: 1–411.
8 Sherrington CS. The correlation of reflexes and the principle of the common path. *Brit Ass Rep* 1904;74:728–41.
9 Walshe FMR. *Chapters I-V: critical studies in neurology*. Edinburgh: E & S Livingstone, 1948: 3–237.
10 Merton PA. Speculations on the servo-control of movement. In: Wolstenholme GEW, ed. *The spinal cord, Ciba Foundation symposium*. Churchill, London, 1953: 247–60.
11 Marsden CD, Merton PA, Morton HB. Servo action in human voluntary movement. *Nature* 1972;238:140–3.
12 Merton PA, man Nin. The first Carmichael memorial lecture. neurophysiology on man. *J Neurol Neurosurg Psychiatry* 1981;44:861–70.
13 Gowers W. *A manual of diseases of the nervous system*. London: J&A Churchill, 1886.
14 Sherrington CS. The mammalian spinal cord as an organ of reflex function. *Philos Trans Roy Soc* 1898;190B:45–186. see also abstract of Croonian Lecture in Proc Roy Soc 1897;61:220-1.
15 Phillips CG, Landau WM. Clinical neuromythology. VIII. Upper and lower motor neuron: the little old synecdoche that works. *Neurology* 1990;40:884–6.
16 Brodal A. *Neurological anatomy in relation to clinical medicine*. Oxford: Oxford University Press, 1981: 180–293.
17 Holstege G. Somatic motoneurons and descending motor pathways: limbic and no-limbic components. In: Leigh PN, Swash M, eds. *Motor neuron disease; biology and management*. London: Springer-Verlag, 1995: 259–330.
18 Lassek AM. The human pyramidal tract. IV. A study of the mature, myelinated fibers of the pyramid. *J Comp Neurol* 1942;76:217–25.
19 Lemon RN. Descending pathways in motor control. *Annu Rev Neurosci* 2008;31:195–218.
20 Jackson JH. Two lectures on hemiplegia. *Lond Hosp Reports* 1865;1:297–32.
21 Babinski MJ. *Sur La reflexe cutanée plantaire dans certaines affections organiques de la systéme nerveux centrale*. Paris: Société de Biologie, 1896: 48. 207–8.
22 Nathan PW, Smith MC. The Babinski response: a review and new observations. *J Neurol Neurosurg Psychiatry* 1955;18:250–9.
23 Wilkins RH, Brody IA. Babinski's sign. *Arch Neurol* 1967;17:441–5.
24 Grillner S, Hellgren J, Ménard A, *et al*. Mechanisms for selection of basic motor programs – roles for the striatum and pallidum. *Trends Neurosci* 2005;28:364–70.
25 Denny-Brown D, Botterell EH. The motor functions of the Agranular frontal cortex. *Res Publ Assoc Res Nerv Ment Dis* 1948;27 (1 vol):235–345.
26 Fulton JF. A note on the definition of the 'frontal' and 'prefrontal' motor areas. *Brain* 1935;58:311–6.
27 Leyton ASF, Sherrington CS. Observations on the excitable cortex of the chimpanzee, orang-utan, and gorilla. *Exp Physiol* 1917;11:135–222.
28 Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 1937;60:389–443.
29 Tower SS. Pyramidal lesion in the monkey. *Brain* 1940;63:36–90.
30 Bucy PC. Is there a pyramidal tract. *Brain* 1957;80:376–92.
31 Bucy PC, Keplinger JE, Siqueira EB. Destruction of the 'Pyramidal Tract' in Man. *J Neurosurg* 1964;21:385–98.
32 Lassek AM, Woolsey CN, Walker AE, *et al*. Symposium of inquiry: the pyramidal tract (moderator, Augustus rose). *Neurology* 1957;7:496–509.
33 Lawrence DG, Kuypers HG. The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. *Brain* 1968;91:1–14.
34 Lawrence DG, Kuypers HG. The functional organization of the motor system in the monkey. II. The effects of lesions of the descending brain-stem pathways. *Brain* 1968;91:15–36.
35 Lemon RN, Landau W, Tutssel D, *et al*. Lawrence and Kuypers (1968a, B) revisited: copies of the original filmed material from their classic papers in brain. *Brain* 2012;135:2290–5.
36 Fetz EE, Cheney PD. Postspike facilitation of forelimb muscle activity by primate corticomotoneuronal cells. *J Neurophysiol* 1980;44:751–72.
37 Nishimura Y, Perlmutter SI, Eaton RW, *et al*. Spike-timing-dependent plasticity in primate corticospinal connections induced during free behavior. *Neuron* 2013;80:1301–9.
38 Perlmutter SI, Maier MA, Fetz EE. Activity of spinal interneurons and their effects on forearm muscles during voluntary wrist movements in the monkey. *J Neurophysiol* 1998;80:2475–94.
39 Lundberg A. Descending control of forelimb movements in the cat. *Brain Res Bull* 1999;50:323–4.
40 Kinoshita M, Matsui R, Kato S, *et al*. Genetic dissection of the circuit for hand dexterity in primates. *Nature* 2012;487:235–8.
41 Pierrot-Deseilligny E. Propriospinal transmission of part of the corticospinal excitation in humans. *Muscle Nerve* 2002;26:155–72.
42 Pierrot-Deseilligny E, Burke D. *The circuitry of the human spinal cord: spinal and corticospinal mechanisms of movement*. New York: Cambridge University Press, 2012: 606.
43 Tohyama T, Kinoshita M, Kobayashi K, *et al*. Contribution of propriospinal neurons to recovery of hand dexterity after corticospinal tract lesions in monkeys. *Proc Natl Acad Sci U S A* 2017;114:604–9.
44 Kugelberg E, Eklund K, Grimby L. An electromyographic study of the nociceptive reflexes of the lower limb. Mechanism of the plantar responses. *Brain* 1960;83:394–410.
45 Swash M. Vulnerability of lower brachial myotomes in motor neurone disease: a clinical and single fibre EMG study. *J Neurol Sci* 1980;47:59–68.
46 Swash M, Leader M, Brown A, *et al*. Focal loss of anterior horn cells in the cervical cord in motor neuron disease. *Brain* 1986;109(Pt 5):939–52.
47 Ravits JM, La Spada AR. ALS phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. *Neurology* 2009;73:805–11.
48 Sekiguchi T, Kanouchi T, Shibuya K, *et al*. Spreading of amyotrophic lateral sclerosis lesions--multifocal hits and local propagation? *J Neurol Neurosurg Psychiatry* 2014;85:85–91.
49 Swash M. How does ALS spread between neurones in the CNS? *J Neurol Neurosurg Psychiatry* 2013;84:116–7.
50 Eisen A, Kuwabara S. The split hand syndrome in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2012;83:399–403.
51 Wilson SAK. Chapter 54: Amyotrophic lateral sclerosis. In: *Neurology*. London: Edward Arnold, 1940: 1007–32.
52 Wilbourn AJ. The 'split hand syndrome' *Muscle Nerve* 2000;23:138.
53 Kuwabara S, Sonoo M, Komori T, *et al*. Dissociated small hand muscle atrophy in amyotrophic lateral sclerosis: frequency, extent, and specificity. *Muscle Nerve* 2008;37:426–30.

54 de Carvalho M, Swash M. The split hand in amyotrophic lateral sclerosis: a possible role for the neuromuscular junction. *Amyotroph Lateral Scler Frontotemporal Degener* 2019;20:368–75.
55 Desai J, Swash M. Extrapyramidal involvement in amyotrophic lateral sclerosis: backward falls and retropulsion. *J Neurol Neurosurg Psychiatry* 1999;67:214–6.
56 Burke D, Wissel J, Donnan GA. Pathophysiology of spasticity in stroke. *Neurology* 2013;80:S20–6.
57 Leiguarda R. Chapter 17: Apraxias as traditionally defined. In: Freund H-J, Jeannerod M, Hallett M, eds. *Higher-Order motor disorders: from neuroanatomy and neurobiology to clinical neurology*. Oxford: Oxford University Press, 2005: 303–38.
58 Liepmann H. Das Krankheitsbild der Apraxie ("motorischen Asymbolie") auf Grund eines Falles von einseitiger Apraxie (Fortsetzung.) pp. 117–132. *Eur Neurol* 1900;8:117–32.
59 Catani M, ffytche DH. The rises and falls of disconnection syndromes. *Brain* 2005;128:2224–39.
60 Marie P. Lectures on diseases of the spinal cord. New Sydenham Society, London, lecture XXXVIII. *Amyotrophic Lateral Sclerosis* 1885:467–74.
61 Charcot JM, Marie P. Deux Nouveau cas de la sclérose amyotrophique latérale suivis d'autopsie. *Arch Neurol* 1885:101–35.
62 Bertrand L, Van Bogaert L. La Sclérose Amyotrophique Latérale (anatomie pathologique). *Rev Neurol* 1925;32:779–806.
63 Davison C. Amyotrophic lateral sclerosis: origin and extent of the upper motor neuron lesion. *Arch NeurPsych* 1941;46:1039–56.
64 Brownell B, Oppenheimer DR, Hughes JT. The central nervous system in motor neurone disease. *J Neurol Neurosurg Psychiatry* 1970;33:338–57.
65 Baker MR. ALS – dying forward, backward or outward? *Nat Rev Neurol* 2014;10:660.
66 Lawyer T, Netsky MG. Amyotrophic lateral sclerosis: a clinico-anatomic study of 53 cases. *Arch Neurol* 1953;69:171–93.
67 Smith MC. Nerve fibre degeneration in the brain in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1960;23:269–82.
68 Martin J, Swash M. Alternative Approaches to the Pathology of Motor Disease. In: Leigh PN, Swash M, eds. *Motor neuron disease: biology and management*. Verlag, London: Springer, 1985: 119–61.
69 Chou S. Pathology of Motor System Disorder. In: Leigh PN, Swash M, eds. *Motor neuron disease: biology and management*. Verlag, London: Springer, 1995: 53–92.
70 Nihei K, McKee AC, Kowall NW. Patterns of neuronal degeneration in the motor cortex of amyotrophic lateral sclerosis patients. *Acta Neuropathol* 1993;86:55–64.
71 Maekawa S, Al-Sarraj S, Kibble M, *et al*. Cortical selective vulnerability in motor neuron disease: a morphometric study. *Brain* 2004;127:1237–51.
72 Gredal O, Pakkenberg H, Karlsborg M, *et al*. Unchanged total number of neurons in motor cortex and neocortex in amyotrophic lateral sclerosis: a stereological study. *J Neurosci Methods* 2000;95:171–6.
73 Cavanagh JB. The problems of neurons with long axons. *The Lancet* 1984;323:1284–7.
74 Ince PG, Evans J, Knopp M, *et al*. Corticospinal tract degeneration in the progressive muscular atrophy variant of ALS. *Neurology* 2003;60:1252–8.
75 Rosenbohm A, Müller H-P, Hübers A, *et al*. Corticoefferent pathways in pure lower motor neuron disease: a diffusion tensor imaging study. *J Neurol* 2016;263:2430–7.
76 Ellis CM, Simmons A, Dawson JM, *et al*. Distinct hyperintense MRI signal changes in the corticospinal tracts of a patient with motor neuron disease. *Amyotroph Lateral Scler Other Motor Neuron Disord* 1999;1:41–4.
77 Adalbert R, Coleman MP. Review: axon pathology in age-related neurodegenerative disorders. *Neuropathol Appl Neurobiol* 2013;39:90–108.
78 Yaron A, Schuldiner O. Common and divergent mechanisms in developmental neuronal remodeling and dying back neurodegeneration. *Curr Biol* 2016;26:R628–39.
79 Conforti L, Gilley J, Coleman MP. Wallerian degeneration: an emerging axon death pathway linking injury and disease. *Nat Rev Neurosci* 2014;15:394–409.
80 Hammer RP, Tomiyasu U, Scheibel AB. Degeneration of the human Betz cell due to amyotrophic lateral sclerosis. *Exp Neurol* 1979;63:336–46.
81 Horoupian DS, Thal L, Katzman R, *et al*. Dementia and motor neuron disease: morphometric, biochemical, and Golgi studies. *Ann Neurol* 1984;16:305–13.
82 Ferrer I. Neurons and their dendrites in frontotemporal dementia. *Dement Geriatr Cogn Disord* 1999;10(Suppl 1):55–60.
83 Genç B, Jara JH, Lagrimas AKB, *et al*. Apical dendrite degeneration, a novel cellular pathology for Betz cells in ALS. *Sci Rep* 2017;7:srep41765.
84 Jara JH, Villa SR, Khan NA, *et al*. AAV2 mediated retrograde transduction of corticospinal motor neurons reveals initial and selective apical dendrite degeneration in ALS. *Neurobiol Dis* 2012;47:174–83.
85 Fogarty MJ, Klenowski PM, Lee JD, *et al*. Cortical synaptic and dendritic spine abnormalities in a presymptomatic TDP-43 model of amyotrophic lateral sclerosis. *Sci Rep* 2016;6:37968.
86 Handley EE, Pitman KA, Dawkins E, *et al*. Synapse dysfunction of layer V pyramidal neurons precedes neurodegeneration in a mouse model of TDP-43 proteinopathies. *Cereb Cortex* 2017;27:3630–47.
87 Broad RJ, Gabel MC, Dowell NG, *et al*. Neurite orientation and dispersion density imaging (NODDI) detects cortical and corticospinal tract degeneration in ALS. *J Neurol Neurosurg Psychiatry* 2019;90:404–11.
88 Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. *N Engl J Med* 2017;377:162–72. and 1602(letter).
89 Olsson B, Portelius E, Cullen NC, *et al*. Association of cerebrospinal fluid neurofilament light protein levels with cognition in patients with dementia, motor neuron disease, and movement disorders. *JAMA Neurol* 2019;76:318–25.
90 Rosengren LE, Karlsson JE, Karlsson JO, *et al*. Patients with amyotrophic lateral sclerosis and other neurodegenerative diseases have increased levels of neurofilament protein in CSF. *J Neurochem* 1996;67:2013–8.
91 Brettschneider J, Petzold A, Sussmuth SD, *et al*. Axonal damage markers in cerebrospinal fluid are increased in ALS. *Neurology* 2006;66:852–6.
92 Lu C-H, Macdonald-Wallis C, Gray E, *et al*. Neurofilament light chain: a prognostic biomarker in amyotrophic lateral sclerosis. *Neurology* 2015;84:2247–57.
93 Verde F, Steinacker P, Weishaupt JH, *et al*. Neurofilament light chain in serum for the diagnosis of amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2019;90:157–64.
94 Feneberg E, Oeckl P, Steinacker P, *et al*. Multicenter evaluation of neurofilaments in early symptom onset amyotrophic lateral sclerosis. *Neurology* 2018;90:e22–30.
95 Poesen K, De Schaepdryver M, Stubendorff B, *et al*. Neurofilament markers for ALS correlate with extent of upper and lower motor neuron disease. *Neurology* 2017;88:2302–9.
96 Pringle CE, Hudson AJ, Munoz DG, *et al*. Primary lateral sclerosis. clinical features, neuropathology and diagnostic criteria. *Brain* 1992;115(Pt 2):495–520.
97 Chang JL, Lomen-Hoerth C, Murphy J, *et al*. A voxel-based morphometry study of patterns of brain atrophy in ALS and ALS/FTLD. *Neurology* 2005;65:75–80.
98 Grosskreutz J, Kaufmann J, Frädrich J, *et al*. Widespread sensorimotor and frontal cortical atrophy in amyotrophic lateral sclerosis. *BMC Neurol* 2006;6:17.
99 Schuster C, Kasper E, Dyrba M, *et al*. Cortical thinning and its relation to cognition in amyotrophic lateral sclerosis. *Neurobiol Aging* 2014;35:240–6.
100 Bede P, Bokde A, Elamin M, *et al*. Grey matter correlates of clinical variables in amyotrophic lateral sclerosis (ALS): a neuroimaging study of ALS motor phenotype heterogeneity and cortical focality. *J Neurol Neurosurg Psychiatry* 2013;84:766–73.
101 Goodin DS, Rowley HA, Olney RK. Magnetic resonance imaging in amyotrophic lateral sclerosis. *Ann Neurol* 1988;23:418–20.
102 Fabes J, Matthews L, Filippini N, *et al*. Quantitative FLAIR MRI in amyotrophic lateral sclerosis. *Acad Radiol* 2017;24:1187–94.
103 Ellis CM, Simmons A, Jones DK, *et al*. Diffusion tensor MRI assesses corticospinal tract damage in ALS. *Neurology* 1999;53:1051–8.
104 Pioro EP, Antel JP, Cashman NR, *et al*. Detection of cortical neuron loss in motor neuron disease by proton magnetic resonance spectroscopic imaging in vivo. *Neurology* 1994;44:1933–8.
105 Stagg CJ, Knight S, Talbot K, *et al*. Whole-brain magnetic resonance spectroscopic imaging measures are related to disability in ALS. *Neurology* 2013;80:610–5.
106 Kassubek J, Unrath A, Huppertz H-J, *et al*. Global brain atrophy and corticospinal tract alterations in ALS, as investigated by voxel-based morphometry of 3-D MRI. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2005;6:213–20.
107 Filippini N, Douaud G, Mackay CE, *et al*. Corpus callosum involvement is a consistent feature of amyotrophic lateral sclerosis. *Neurology* 2010;75:1645–52.
108 Probst M. *Zur Kenntnis Der amyotrophischen Lateralsklerose*. . S-B Akad Wiss Wien, 1903: 112. 683–824.
109 Iwata NK, Aoki S, Okabe S, *et al*. Evaluation of corticospinal tracts in ALS with diffusion tensor MRI and brainstem stimulation. *Neurology* 2008;70:528–32.
110 Agosta F, Galantucci S, Riva N, *et al*. Intrahemispheric and interhemispheric structural network abnormalities in PLS and ALS. *Hum Brain Mapp* 2014;35:1710–22.
111 Sach M, Winkler G, Glauche V, *et al*. Diffusion tensor MRI of early upper motor neuron involvement in amyotrophic lateral sclerosis. *Brain* 2004;127:340–50.
112 Cardenas AM, Sarlls JE, Kwan JY, *et al*. Pathology of callosal damage in ALS: An *ex-vivo*, 7 T diffusion tensor MRI study. *Neuroimage Clin* 2017;15:200–8.
113 Pallebage-Gamarallage M, Foxley S, Menke RAL, *et al*. Dissecting the pathobiology of altered MRI signal in amyotrophic lateral sclerosis: a post mortem whole brain sampling strategy for the integration of ultra-high-field MRI and quantitative neuropathology. *BMC Neurosci* 2018;19:11.
114 Menke RAL, Körner S, Filippini N, *et al*. Widespread grey matter pathology dominates the longitudinal cerebral MRI and clinical landscape of amyotrophic lateral sclerosis. *Brain* 2014;137:2546–55.
115 Tu S, Menke RAL, Talbot K, *et al*. Regional thalamic MRI as a marker of widespread cortical pathology and progressive frontotemporal involvement in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2018;89:1250–8.
116 Verstraete E, Turner MR, Grosskreutz J, *et al*. Mind the gap: the mismatch between clinical and imaging metrics in ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;16:524–9.
117 Dalakas MC, Hatazawa J, Brooks RA, *et al*. Lowered cerebral glucose utilization in amyotrophic lateral sclerosis. *Ann Neurol* 1987;22:580–6.
118 Van Laere K, Vanhee A, Verschueren J, *et al*. Value of 18fluorodeoxyglucose-positron-emission tomography in amyotrophic lateral sclerosis: a prospective study. *JAMA Neurol* 2014;71:553–61.

119 Kew JJ, Leigh PN, Playford ED, *et al*. Cortical function in amyotrophic lateral sclerosis. A positron emission tomography study. *Brain* 1993;116(Pt 3):655–80.
120 Turner MR, Hammers A, Al-Chalabi A, *et al*. Distinct cerebral lesions in sporadic and 'D90A' SOD1 ALS: studies with [11C]flumazenil PET. *Brain* 2005;128:1323–9.
121 Douaud G, Filippini N, Knight S, *et al*. Integration of structural and functional magnetic resonance imaging in amyotrophic lateral sclerosis. *Brain* 2011;134:3470–9.
122 Foerster BR, Callaghan BC, Petrou M, *et al*. Decreased motor cortex γ-aminobutyric acid in amyotrophic lateral sclerosis. *Neurology* 2012;78:1596–600.
123 Seeley WW, Crawford RK, Zhou J, *et al*. Neurodegenerative diseases target large-scale human brain networks. *Neuron* 2009;62:42–52.
124 Eisen A, Turner MR. Does variation in neurodegenerative disease susceptibility and phenotype reflect cerebral differences at the network level? *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14:487–93.
125 Menke RAL, Proudfoot M, Wuu J, *et al*. Increased functional connectivity common to symptomatic amyotrophic lateral sclerosis and those at genetic risk. *J Neurol Neurosurg Psychiatry* 2016;87:580–8.
126 Proudfoot M, Rohenkohl G, Quinn A, *et al*. Altered cortical beta-band oscillations reflect motor system degeneration in amyotrophic lateral sclerosis. *Hum Brain Mapp* 2017;38:237–54.
127 Proudfoot M, van Ede F, Quinn A, *et al*. Impaired corticomuscular and interhemispheric cortical beta oscillation coupling in amyotrophic lateral sclerosis. *Clin Neurophysiol* 2018;129:1479–89.
128 Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. *Nature* 1980;285:227.
129 Ingram DA, Swash M. Central motor conduction is abnormal in motor neuron disease. *J Neurol Neurosurg Psychiatry* 1987;50:159–66.
130 Berardelli A, Inghilleri M, Formisano R, *et al*. Stimulation of motor tracts in motor neuron disease. *J Neurol Neurosurg Psychiatry* 1987;50:732–7.
131 Hugon J, Lubeau M, Tabaraud F, *et al*. Central motor conduction in motor neuron disease. *Ann Neurol* 1987;22:544–6.
132 Barker AT, Freeston IL, Jalinous R, *et al*. Clinical evaluation of conduction time measurements in central motor pathways using magnetic stimulation of human brain. *The Lancet* 1986;327:1325–6.
133 Schriefer TN, Hess CW, Mills KR, *et al*. Central motor conduction studies in motor neurone disease using magnetic brain stimulation. *Electroencephalogr Clin Neurophysiol* 1989;74:431–7.
134 Eisen A, Shytbel W, Murphy K, *et al*. Cortical magnetic stimulation in amyotrophic lateral sclerosis. *Muscle Nerve* 1990;13:146–51.
135 Triggs WJ, Menkes D, Onorato J, *et al*. Transcranial magnetic stimulation identifies upper motor neuron involvement in motor neuron disease. *Neurology* 1999;53:605–11.
136 Caramia MD, Cicinelli P, Paradiso C, *et al*. 'Excitability' changes of muscular responses to magnetic brain stimulation in patients with central motor disorders. *Electroencephalogr Clin Neurophysiol* 1991;81:243–50.
137 Desiato MT, Caramia MD. Towards a neurophysiological marker of amyotrophic lateral sclerosis as revealed by changes in cortical excitability. *Electroencephalogr Clin Neurophysiol* 1997;105:1–7.
138 Eisen A, Pant B, Stewart H. Cortical excitability in amyotrophic lateral sclerosis: a clue to pathogenesis. *Can J Neurol Sci* 1993;20:11–16.
139 Yokota T, Yoshino A, Inaba A, *et al*. Double cortical stimulation in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1996;61:596–600.
140 Ziemann U, Winter M, Reimers CD, *et al*. Impaired motor cortex inhibition in patients with amyotrophic lateral sclerosis. Evidence from paired transcranial magnetic stimulation. *Neurology* 1997;49:1292–8.
141 Vucic S, van den Bos M, Menon P, *et al*. Utility of threshold tracking transcranial magnetic stimulation in ALS. *Clin Neurophysiol Pract* 2018;3:164–72.
142 Vucic S, Lin CS-Y, Cheah BC, *et al*. Riluzole exerts central and peripheral modulating effects in amyotrophic lateral sclerosis. *Brain* 2013;136:1361–70.
143 Kohara N, Kaji R, Kojima Y, *et al*. Abnormal excitability of the corticospinal pathway in patients with amyotrophic lateral sclerosis: a single motor unit study using transcranial magnetic stimulation. *Electroencephalogr Clin Neurophysiol* 1996;101:32–41.
144 de Carvalho M, Miranda PC, Lourdes Sales Luís M, *et al*. Neurophysiological features of fasciculation potentials evoked by transcranial magnetic stimulation in amyotrophic lateral sclerosis. *J Neurol* 2000;247:189–94.
145 Floeter MK, Zhai P, Saigal R, *et al*. Motor neuron firing dysfunction in spastic patients with primary lateral sclerosis. *J Neurophysiol* 2005;94:919–27.
146 de Carvalho M, Turkman A, Swash M. Motor unit firing in amyotrophic lateral sclerosis and other upper and lower motor neurone disorders. *Clin Neurophysiol* 2012;123:2312–8.
147 Chen R, Lozano AM, Ashby P. Mechanism of the silent period following transcranial magnetic stimulation. Evidence from epidural recordings. *Exp Brain Res* 1999;128:539–42.
148 Siciliano G, Manca ML, Sagliocco L, *et al*. Cortical silent period in patients with amyotrophic lateral sclerosis. *J Neurol Sci* 1999;169:93–7.
149 Simon NG, Lin CS-Y, Lee M, *et al*. Segmental motoneuronal dysfunction is a feature of amyotrophic lateral sclerosis. *Clin Neurophysiol* 2015;126:828–36.
150 Sangari S, Iglesias C, El Mendili M-M, *et al*. Impairment of sensory-motor integration at spinal level in amyotrophic lateral sclerosis. *Clin Neurophysiol* 2016;127:1968–77.
151 Fisher KM, Zaaimi B, Williams TL, *et al*. Beta-Band intermuscular coherence: a novel biomarker of upper motor neuron dysfunction in motor neuron disease. *Brain* 2012;135:2849–64.
152 Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum - insights from the clinic. *Cerebellum* 2007;6:254–67.