

Testing upper motor neuron function in amyotrophic lateral sclerosis: the most difficult task of neurophysiology

Clinical signs of upper motor neuron involvement are an essential observation to support the diagnosis of amyotrophic lateral sclerosis. However, clinical signs of upper motor neuron can be difficult to elicit in patients with motor neuron disease. One postulated reason for this problem is the presence of marked limb weakness and amyotrophy in motor neuron disease. This has been observed in patients with genetic mutations and clear-cut pathological evidence of upper and lower motor neuron degeneration. Less commonly, it has been recognized that the pattern of upper motor neuron lesion in amyotrophic lateral sclerosis is rather different from other conditions, in which there is damage to other descending motor fibres from extra-Rolandic motor cortical areas (Swash, 2012). In particular, the impact of the concomitant α and γ spinal motor neuron loss and of spinal interneuron degeneration on the expression of the usual signs of upper motor neuron lesion are not well known (Swash, 2012). Probably, other clinical signs suggesting upper motor neuron dysfunction, such as mirror movements or the presence of apraxia, should be explored to support corticomo-tor involvement in motor neuron disease.

Over the years, different techniques have been developed that help the neurologist to identify, measure and understand the upper motor neuron lesion in amyotrophic lateral sclerosis. Many transcranial magnetic stimulation methods have been used in this context to investigate integrity of the motor cortex and its descending pathways. A number of results reflecting delayed central conduction time and reduced motor-evoked potential amplitude indicate corticospinal tract damage (de Carvalho *et al.*, 2003). Nonetheless, in amyotrophic lateral sclerosis, there is strong evidence for increased cortical excitability in early phases of the disease progression, suggesting either an initial phase in which the lower motor neuron demise is compensated or representing the initial pathogenic disturbance leading to lower motor neuron dysfunction (Vucic and Kiernan, 2006). Nevertheless, the combination of positive (increased cortical excitability) and negative (delayed central conduction time and reduced motor response) findings make transcranial magnetic stimulation a difficult technique with which to document serial upper motor neuron degeneration. Many groups have devoted much time and effort seeking the most sensitive and simple neuroimaging technique for detection of the upper motor neuron lesion in motor neuron disease. Voxel-based morphometry has been inconsistent in measuring the motor area; surface-based morphometry reveals cortical thinning in the precentral gyrus, but with a poor correlation with clinical findings; fractional anisotropy as evaluated by diffusion tensor imaging is one promising approach, but shows non-specific changes, and its usefulness to quantify progression is not clear; magnetic resonance spectroscopy is sensitive to motor cortex pathology, but the studies using this method have been inconclusive; functional MRI with blood oxygenation level-dependent

contrast is potentially very effective for exploring neuronal inter-connection dysfunction in amyotrophic lateral sclerosis, but still needs more investigation; and novel neuroinflammatory and inhibitory positron emission tomography ligands might have utility in the future (Turner, 2012). However, expense and practical issues limit the use of these sophisticated imaging techniques to a few highly specialized centres. Thus far, therefore, no method to investigate upper motor neuron function has proved useful and applicable as a measure of efficacy in clinical trials, despite some enthusiasm for the threshold tracking transcranial magnetic stimulation as a marker of early diagnosis.

EMG is also not the preferred method for assessing upper motor neuron dysfunction, although some F-waves and H-reflex measurements and firing-rate analysis (de Carvalho *et al.*, 2012) represent interesting developments. However, an exciting new window for EMG as a way to test upper motor neuron function has been opened by coherence analysis.

In the past, a number of studies have investigated oscillatory activity of ~15–30 Hz in the primary motor cortex both in humans (Conway *et al.*, 1995) and monkeys using local field potential recordings (Murthy and Fetz, 1996). Indeed, cortically driven muscle contraction originates beta frequency oscillation synchronization between cortex and contralateral muscles, as well as between individual muscles (intermuscular coherence), as identified many years ago in animal studies (Baker *et al.*, 1997). Experimental evidence shows that this oscillation is generated by Layer V of the motor cortex (Roopun *et al.*, 2006). Cross-correlation analysis to study the firing pattern of the motor units showed that patients with stroke and spinal cord injury have abnormal motor unit synchronization (Farmer *et al.*, 1993). In this issue of *Brain*, Fisher and co-authors describe their experience investigating intermuscular coherence in the 15–30-Hz range in controls and in patients with progressive muscle atrophy or primary lateral sclerosis. In summary, significant beta-band coherence was observed in all control subjects and all patients with progressive muscular atrophy tested, but not in those with primary lateral sclerosis. The authors conclude that intermuscular coherence in the 15–30-Hz range is dependent on an intact corticospinal tract, whereas it is not substantially altered by loss of anterior horn cells. These results are very stimulating and open a new avenue for investigation. Although this report has some limitations—including the small number of subjects, unilateral recording and the absence of systematic longitudinal evaluation (limited to one case)—it is evident that the study will have great impact on the field. It will now be possible inexpensively to investigate upper motor neuron function using standard EMG equipment and the appropriate software in any neurological centre. To complement this information by investigating corticomuscular coherence with EEG recording is an exciting possibility (Mima and Hallet, 1999).

In recent times, progress in computational science has led to a resurgence of interest in brain oscillations. This development permits the investigation of neuronal connectivity and its modulation, together with the implications for motor system, cognitive, brain plasticity and behavioural physiology. The expansion of modulation research to corticomuscular and intermuscular coherence analysis now also offers clinical neurophysiology as a tool for testing the impact of treatment intervention on upper motor neuron function in degenerative disease of the human CNS.

Mamede de Carvalho
 Instituto de Medicina Molecular, Faculty of Medicine,
 University of Lisbon,
 Lisbon, Portugal

Correspondence to: Mamede de Carvalho,
 Institute of Physiology,
 Faculty of Medicine-University of Lisbon,
 Avenida Professor Egas Moniz, 1648-029 Lisbon,
 Portugal
 E-mail: mamedemg@mail.telepac.pt

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References

Baker SN, Olivier E, Lemon RN. Coherent oscillations in monkey motor cortex and hand muscle EMG show task-dependent modulation. *J Physiol* 1997; 501: 225–41.

- Conway BA, Halliday DM, Farmer SF, Shahani U, Maas P, Weir AJ, et al. Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. *J Physiol* 1995; 489: 917–24.
- de Carvalho M, Turkman A, Swash M. Motor responses evoked by transcranial magnetic stimulation and peripheral nerve stimulation in the ulnar innervation in amyotrophic lateral sclerosis: the effect of upper and lower motor neuron lesion. *J Neurol Sci* 2003; 210: 83–90.
- 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 May [Epub ahead of print] PMID: 22627021.
- Mima T, Hallett M. Electroencephalographic analysis of cortico-muscular coherence; reference effect, volume conduction and generator mechanism. *Clin Neurophysiol* 1999; 100: 1892–9.
- Murthy VN, Fetz EE. Oscillatory activity in sensorimotor cortex of awake monkeys: synchronization of local field potentials and relation to behavior. *J Neurophysiol* 1996; 76: 3349–67.
- Roopun AK, Middleton SJ, Cunningham MO, LeBeau FE, Bibbig A, Whittington MA, et al. A beta2-frequency (20–30 Hz) oscillation in nonsynaptic networks of somatosensory cortex. *Proc Natl Acad Sci USA* 2006; 103: 15646–50.
- Swash M. Why are upper motor neuron signs difficult to elicit in amyotrophic lateral sclerosis? *J Neurol Neurosurg Psychiatry* 2012; 83: 659–62.
- Turner M, Agosta F, Bede P, Govind V, Lulé D, Verstraete E. Neuroimaging in amyotrophic lateral sclerosis. *Biomark Med* 2012; 6: 319–27.
- Vucic S, Kiernan MC. Novel threshold tracking techniques suggest that cortical hyperexcitability is an early feature of motor neuron disease. *Brain* 2006; 129: 2436–46.

Delirium, dementia and senility

Delirium is a neuropsychiatric syndrome characterized by sudden onset and global effects on degrees of consciousness, attention and cognition. It is now widely recognized that delirium is associated with high morbidity and mortality. Increasing age appears the strongest risk factor for delirium (Table 1). It affects up to 40% of all medically ill older adults. Delirium subsequent to surgical procedures, particularly those involving major fractures, cardiovascular grafting or organ transplantation is unpredictable, ranging 9–87% with an average of 40%, depending on the age of the patient, type of intervention and pre-existing vascular disease risks or infections (Cerejeira and Mukaetova-Ladinska, 2011). The presence of delirium complicates outcomes in the majority of ill patients, as demonstrated by longer hospital admission, and impact on daily performance, frequently leading to costly institutional care. In all these situations, it is necessary to ensure that delirium is consistently and correctly diagnosed. Being well qualified to make the diagnosis—as psychiatrist, neurologist or geriatrician—is an important consideration when reporting on the nature or consequences of delirium in any particular study.

Cognitive changes after episodes of delirium

Over and above the established immediate consequences, there also appears to be a link between delirium and long-term cognitive impairment (MacLulich *et al.*, 2009; Witlox *et al.*, 2010; de Lange *et al.*, 2012). Despite varied sample sizes, study designs, screening methods and origin of patients being studied, there is remarkable consistency of evidence that even a single episode of delirium is detrimental to cognitive function and may more than double the risk of dementia (Witlox *et al.*, 2010). An increased risk of poor cognitive outcome and dementia is particularly noteworthy in older adults who have had a prolonged episode of delirium lasting weeks to months (MacLulich *et al.*, 2009), irrespective of gender, co-morbidity, illness severity or presence of dementia at baseline. Conversely, cognitive impairment is itself one of the recognized risk factors for delirium. The prevalence of delirium is estimated at up to 70% in institutionalized people with dementia (de Lange *et al.*, 2012). Others have observed the incidence of delirium at