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Beta-band intermuscular coherence: a novel biomarker of upper motor neuron dysfunction in motor neuron disease

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In motor neuron disease, the focus of therapy is to prevent or slow neuronal degeneration with neuroprotective pharmacological agents; early diagnosis and treatment are thus essential. Incorporation of needle electromyographic evidence of lower motor neuron degeneration into diagnostic criteria has undoubtedly advanced diagnosis, but even earlier diagnosis might be possible by including tests of subclinical upper motor neuron disease. We hypothesized that beta-band (15–30 Hz) intermuscular coherence could be used as an electrophysiological marker of upper motor neuron integrity in such patients. We measured intermuscular coherence in eight patients who conformed to established diagnostic criteria for primary lateral sclerosis and six patients with progressive muscular atrophy, together with 16 age-matched controls. In the primary lateral sclerosis variant of motor neuron disease, there is selective destruction of motor cortical layer V pyramidal neurons and degeneration of the corticospinal tract, without involvement of anterior horn cells. In progressive muscular atrophy, there is selective degeneration of anterior horn cells but a normal corticospinal tract. All patients with primary lateral sclerosis had abnormal motor-evoked potentials as assessed using transcranial magnetic stimulation, whereas these were similar to controls in progressive muscular atrophy. Upper and lower limb intermuscular coherence was measured during a precision grip and an ankle dorsiflexion task, respectively. Significant beta-band coherence was observed in all control subjects and all patients with progressive muscular atrophy tested, but not in the patients with primary lateral sclerosis. We conclude that intermuscular coherence in the 15–30 Hz range is dependent on an intact corticospinal tract but persists in the face of selective anterior horn cell destruction. Based on the distributions of coherence values measured from patients with primary lateral sclerosis and control subjects, we estimated the likelihood that a given measurement reflects corticospinal tract degeneration. Therefore, intermuscular coherence has potential as a quantitative test of subclinical upper motor neuron involvement in motor neuron disease.

Keywords: corticospinal; intermuscular coherence; oscillations; motor neuron disease; amyotrophic lateral sclerosis

Introduction

Motor neuron disease is a sporadic, fatal, neurodegenerative disorder. It is a rare condition, with an estimated incidence of 2.4–3.9 people affected in every 100 000 (Dean *et al.*, 1994; Alonso *et al.*, 2009; Logroscino *et al.*, 2010), and includes a spectrum of conditions, the most common of which is amyotrophic lateral sclerosis. This is characterized by widespread degeneration of motor neurons within the brainstem and ventral horn of the spinal cord, in addition to destruction of layer V pyramidal neurons of the motor cortex. Amyotrophic lateral sclerosis is typically an aggressive and rapidly progressive form of motor neuron disease (average life expectancy of 2.5 years from diagnosis). Diagnosis is dependent on the presence of upper motor neuron and lower motor neuron pathology in multiple regions (bulbar, cervical, thoracic and lumbosacral), according to the El Escorial criteria (Brooks, 1994), after excluding other potentially treatable causes. The El Escorial criteria were first revised in 1997 (Miller *et al.*, 1999) and again in 2006 (Carvalho and Swash, 2009) to include, with increasing emphasis, preclinical evidence on EMG of lower motor neuron disease outside regions identified clinically. This requires documentation of EMG changes indicative of denervation in at least two muscles innervated by different roots and nerves, in at least two separate anatomical regions. As a consequence, the revised criteria have permitted earlier diagnosis of motor neuron disease where lower motor neuron pathology is a primary feature.

Early diagnosis is important in a disease in which the primary strategy of treatment is to halt or slow the relentless degeneration of motor neurons. Unfortunately, even at symptomatic presentation, when the diagnosis is often uncertain, there is already extensive motor neuron degeneration. Studies suggest that these patients lose up to 50% of motor units before a muscle becomes symptomatically weak (Hansen and Ballantyne, 1978; Aggarwal and Nicholson, 2002). This presents problems for clinical trials of neuroprotective agents. First, because of extensive neuronal destruction, the population of salvageable motor neurons is small; at trial recruitment, <5% of motor units remain in overtly affected (i.e. weak and wasted) muscle and between 25% and 50% in some clinically unaffected muscles (Hansen and Ballantyne, 1978; Aggarwal and Nicholson, 2002). Second, identifying statistically significant changes in endpoints such as strength and disability will be difficult because effects will be small in patients who may already be very weak and disabled at enrolment. Surprisingly, despite this, early trials of riluzole in patients with amyotrophic lateral sclerosis demonstrated small but significant benefits (Bensimon *et al.*, 1994; Lacomblez *et al.*, 1996; Miller *et al.*, 2007). The effects of riluzole on progression and survival might be even greater if it could be administered earlier in the disease course, before significant cell loss had occurred.

The diagnosis of motor neuron disease is somewhat limited by our inability to assess reliably the integrity of the corticospinal tract, which is particularly difficult in the presence of extensive anterior horn cell disease. Clinically, there are useful indicators of corticospinal tract damage including the Babinski sign and hyperreflexia; however, these may not solely reflect pathology restricted to the corticospinal tract (Brown, 1994). Transcranial magnetic stimulation has been assimilated into the diagnostic criteria for primary lateral sclerosis (a pure upper motor neuron variant of motor neuron disease) as a test of corticospinal tract function (Pringle *et al.*, 1992); accepted abnormalities include small or absent motor-evoked potentials or prolonged central motor conduction times. Magnetic stimulation has also been used in the more common variants of motor neuron disease to aid diagnosis, but its usefulness has been questioned (Mills, 2003), not least because of a requirement for expensive equipment and the necessary expertise. The triple stimulation technique has increased the diagnostic sensitivity of magnetic stimulation in motor neuron disease (Magistris *et al.*, 1998, 1999) but is uncomfortable and time consuming. Further attempts to quantify corticospinal tract integrity include methods using magnetic resonance spectroscopy (Pohl *et al.*, 2001; Mitsumoto *et al.*, 2007) and MRI tractography (Ciccarelli *et al.*, 2006). However, these methods require expensive MRI systems with specifications and expertise that are also not universally available.

An alternative method to assess upper motor neuron integrity could be to investigate the propagation of oscillatory activity. Rhythmic activity can be recorded from the motor cortex in both animals (Murthy and Fetz, 1996; Baker *et al.*, 1997; Donoghue *et al.*, 1998) and human subjects (Salmelin and Hari, 1994; Halliday *et al.*, 1998) in the alpha (8–12 Hz) and beta (15–30 Hz) frequency bands. Coherence analysis reveals that only beta frequency oscillations are synchronized between cortex and contralateral EMG, suggesting that these oscillations are transmitted from cortex to muscle (Conway *et al.*, 1995; Murthy and Fetz, 1996; Baker *et al.*, 1997, 1999; Salenius *et al.*, 1997; Halliday *et al.*, 1998; Kilner *et al.*, 2000).

In normal subjects, beta-band coupling can also be observed between muscles (intermuscular coherence), demonstrating a shared cortical drive. Intermuscular coherence is maximal during a sustained muscle contraction (Baker *et al.*, 1997; Norton and Gorassini, 2006) and seems to be dependent on supraspinal structures, including the corticospinal tract, because it disappears after stroke and complete spinal cord injury (Farmer *et al.*, 1993; Norton *et al.*, 2003, 2004; Hansen *et al.*, 2005). Moreover, in partial spinal cord injury where some corticospinal fibres may be spared, physical therapy can increase not only functional recovery and motor-evoked potential amplitudes but also 15–30 Hz intermuscular coherence (Norton and Gorassini, 2006). Alpha-band intermuscular coherence can also sometimes be observed in healthy subjects; however, this is likely to be largely dependent on segmental or spinal mechanisms because it persists after complete spinal cord lesions (Norton *et al.*, 2003, 2004).

The extent to which the corticospinal tract contributes to human corticomuscular and intermuscular coherence in the 15–30 Hz range is somewhat controversial. Although some studies have identified phase lags between cortex and muscle that might be consistent with conduction via the fastest corticospinal axons (Gross *et al.*, 2000; Marsden *et al.*, 2000; Mima *et al.*, 2000) and therefore corticofugal propagation of oscillations, others have not (Conway *et al.*, 1995). Studies in which 15–30 Hz oscillations have been disrupted, or reset by stimulating the corticospinal tract (Jackson *et al.*, 2002; Hansen and Nielsen, 2004), have been presented as further evidence of a corticofugal hierarchy for

15–30 Hz oscillations (Hansen and Nielsen, 2004). However, recent work has revealed the important contribution of afferent feedback pathways to corticomuscular coherence (Riddle and Baker, 2005; Baker *et al*., 2006) and demonstrated that activity in the somatosensory cortex also shows corticomuscular coherence (Brovelli *et al*., 2004; Witham *et al*., 2010, 2011).

To determine whether intermuscular coherence is a useful biomarker of upper motor neuron dysfunction, we must first test whether the technique can discriminate between upper and lower motor neuron lesions. In this article, we examine this using two variants of motor neuron disease, which initially present as either pure upper or lower motor neuron disorders. Progressive muscular atrophy, which affects ∼5–10% of patients with motor neuron disease, is a degenerative condition that is initially limited to spinal motor neurons. By contrast, in primary lateral sclerosis, there is selective degeneration of layer V pyramidal neurons (Betz cells) within the precentral gyrus and corticospinal tract axons, but with preservation of anterior horn cells (Pringle *et al*., 1992; Le Forestier *et al*., 2001; Gordon *et al*., 2006). Although in both primary lateral sclerosis and progressive muscular atrophy, hand function is impaired and foot movements are slow and weak, there is usually sufficient residual function to perform simple repetitive manual and pedal tasks. Therefore, these two conditions allow us to address whether coherence reflects corticospinal tract integrity and could be considered as a biomarker of upper motor neuron dysfunction.

Materials and methods

Subjects

Some recordings reported in this article were made as part of routine neurophysiological investigations in patients required for diagnostic work-up. The remaining recordings from patients were gathered in a dedicated research study, approved by a National Research Ethics Service Committee. Studies in control subjects were approved by the Research Ethics Committee of the Medical Faculty, Newcastle University. In all cases, informed consent was obtained before investigation in accordance with the Declaration of Helsinki.

In eight patients (six males, two females; age range: 42–75 years, mean age: 57.9 years), a diagnosis of primary lateral sclerosis had been made after excluding other causes, (Table 1) according to previously published diagnostic criteria (Pringle *et al*., 1992). Investigations included normal structural imaging, normal motor and sensory nerve conduction studies, normal somatosensory-evoked potentials (not performed in patients with progressive muscular atrophy), normal CSF (oligoclonal bands) and a minimum disease duration of 3 years without either clinical or neurophysiological evidence of anterior horn cell disease.

Six patients with a diagnosis of progressive muscular atrophy (four males, two females; age range: 61–73 years, mean age: 66.7 years) were also investigated (Table 2). The diagnosis of progressive muscular atrophy is one of exclusion; patients had electrophysiological evidence of lower motor neuron degeneration in the absence of upper motor neuron signs, a progressive course and no structural, immunological or known genetic explanation for their clinical presentation. Therefore, according to El Escorial criteria (Brooks, 1994), patients with

progressive muscular atrophy are classified as suspected amyotrophic lateral sclerosis.

Control data were obtained from 16 age-matched normal human subjects (eight males, eight females; age range: 47–78 years, mean age: 62.2 years), with no history of neurological abnormality.

Recordings

In the upper limb, surface EMG recordings (electrodes: Bio-logic M0476, Natus Europe GmbH) were made from the first dorsal interosseous, extensor digitorum communis and flexor digitorum superficialis muscles. To ensure that cooling did not affect coherence measurements (Riddle and Baker, 2005), surface EMG recording was acquired with a skin temperature of $>34°C$ (i.e. with muscle and nerve temperature of ∼37°C) in all subjects (according to standard clinical practice). In the majority of cases, we recorded from the side of the body most affected by the disease, although where patients presented with bilateral impairment, we used the dominant hand.

In the lower limb, EMG recordings were made from extensor digitorum brevis, tibialis anterior and gastrocnemius-soleus. Two patients with primary lateral sclerosis (Patients RC and JH) and one patient with progressive muscular atrophy (Patient HR) were unable to perform this lower limb task. Control data were pooled from other studies that were primarily investigating hand function so that only 12/16 subjects performed the lower limb task.

Signals were amplified (gain 500–5000, band pass 30 Hz–2 kHz) and digitized at 5-kHz sampling rate by a Power1401 interface (CED Ltd) and Spike2 software, together with signals indicating the time of trial onset and occurrence of auditory cues.

In addition to EMG recordings, we also measured differential EEG from the contralateral sensorimotor cortex using electrodes placed 30 mm lateral and 20 mm anterior and posterior to the vertex for upper limb recordings (Baker and Baker, 2003; Riddle and Baker, 2006; Witham *et al*., 2011) and placed over vertex and 20 mm anterior to vertex for lower limb recordings. However, we found that significant corticomuscular (EEG–EMG) coherence in the beta-band was not a consistent finding among our cohort of healthy subjects, in agreement with previous studies (Ushiyama *et al*., 2011). As our aim was to measure the reduction in coherence caused by disease processes, in this article, we do not consider results from corticomuscular coherence further.

Motor-evoked potentials

Motor-evoked potentials were obtained using a Magstim 200 stimulator (The Magstim Co Ltd) to deliver transcranial magnetic stimulation over motor cortex. A 13-cm outside diameter circular coil was used for obtaining upper limb motor-evoked potentials; current direction was optimized for stimulation of each hemisphere (A side up: left hemisphere; B side up: right hemisphere). Lower limb motor-evoked potentials were elicited via a double cone coil; again, the coil was oriented to produce the optimal current direction (posterior coil current: left hemisphere; anterior coil current: right hemisphere). In both cases, the coil was centred over the vertex and held in place by hand. Stimuli were delivered at 0.2 Hz.

Active motor threshold was identified in the first dorsal interosseous muscle while subjects provided a gentle background contraction; this was achieved by opposing index finger and thumb. Threshold was defined as the percentage of maximum stimulator output that produced a motor-evoked potential in around half of the stimuli. Recordings used an intensity 10% maximum stimulator output above threshold to elicit well-formed large motor-evoked potentials

Table 1 Details of patients with primary lateral sclerosis

Patient	Sex	Age at diagnosis (years)	HPC at Δ (years)	Initial presentation	Medical history	Drug history	Family history (HSP)	Bladder function	Investigations Laboratory tests	CSF (OCBs)	EMG/ NCS/SEPs	MRI Brain	c-spine	MEPs
1 (RC)	M	49	4	RUL weakness	Nil	Nil	Nil	NAD	Normal B12 VDRL negative	NAD (absent)	NAD	Rolandic atrophy	NAD	UL and LL absent
2 (AB)	F	66	4	LL and LUL spasticity	LVH	Bisoprolol Diclofenac Fluoxetine Baclofen Dantrolene Oxybutinin Quinine Riluzole Vit C and E	Nil	Frequency	Normal B12. HTLV1, VDRL, *Borrelia burgdorferi* serology negative.	NAD (absent)	NAD	NAD	NAD	R UL MEP ↓V L UL and LL MEPs absent
3 (PD)	M	52	18	LL spasticity (R > L)	HD aged 20 (DXT + splenectomy)	Vit C and E	Nil	NAD	Normal VLCFA, WBC enzymes	NAD (absent)	NAD	NAD	NAD	R EDC and R GS absent. MEPs ↓V and ↑CMCT
4 (AM)	M	45	3	LL spasticity (L > R) Pseudobulbar Dysarthria	DM II Hypertension R Sciatica	Lisinopril Quinine Baclofen Riluzole Vit C and E	Nil	NAD	Normal B12, VLCFA, WBC enzymes, VDRL negative	NAD (absent)	NAD (except Lulnar neuropathy, denervation L T7 paraspinal)	NAD	NAD	R FDS and R LL MEPs absent R FDI and R EDC MEPs ↓V and ↑CMCT
5 (GM)	M	75	5	LL spasticity (L > R)	L sciatica	BFMTZ Baclofen Riluzole Vit C and E	Nil	NAD	Normal B12, VLCFA, WBC enzymes	NAD (absent)	NAD (except chronic L L4/L5 radiculopathic changes)	NAD	NAD	R EDC, R EDB and R GS MEPs absent R FDI MEP ↓V R TA MEP ↓V and ↑CMCT
6 (JH)	M	60	5	Pseudobulbar dysarthria L UL and LL spasticity	IHD Colonic carcinoma 1999 Hypertension	Amitriptyline Baclofen Atorvastatin	Nil	NAD	–	NAD (absent)	NAD (except L L5 radiculopathy)	NAD	NAD	R FDS, R EDC absent R FDI long latency and polyphasic
7 (CC)	F	42	2	Progressive spastic paraparesis	Nil	Sertraline Femulen Riluzole	Nil	NAD	B12 normal Normal VLCFA, WBC enzymes, SPAST(SPG4), ATL1	Protein 0.54 g/L (absent)	–	NAD	C5/C6 disc-osteophyte complex (no neural compression)	R EDC and R GS MEPs absent R FDI, FDS, TA and ED B MEPs ↑CMCT and ↓V
8 (JT)	M	74	3.5	Progressive R LL weakness	BPH	Nil	Nil	Bladder outflow obstruction and urgency	Copper normal Autoantibodies negative B12 normal		NAD	Mild involutional change. Minor small vessel CVD	Multilevel degenerative changes, no neural compromise	Normal UL MEPs

BFMTZ = bendroflumethiazide; BPH = benign prostatic hyperplasia; CMCT = ; CVD = ; DMII = type II diabetes mellitus; DXT = radiotherapy; ED = ; EDC = extensor digitorum communis; EMG/NCS = electromyogram/nerve conduction studies; F = female; FDI = first dorsal interosseous; FDS = flexor digitorum superficialis; GS = gastrocnemius/soleus; HD = Hodgkin's disease; HPC = history of presenting complaint; HTLV1 = human T lymphotropic virus; IHD = ischaemic heart disease; L = left; LL = lower limb; LVH = left ventricular hypertrophy; M = male; MEPs = motor evoked potentials; MI = myocardial infarction; NAD = no abnormality detected; OCBs = oligoclonal bands; R = right; Rx = treatment; TA = tibialis anterior; UL = upper limb; V = voltage; VDRL = venereal disease research laboratory; VLCFA = very long chain fatty acids; WBC = white blood cell.

Table 2 Details of patients with progressive muscular atrophy

Patient	Sex	Age at diagnosis (years)	HPC at Δ (months)	Initial presentation	Medical history	Drug history	Family history (HSP)	Bladder function	Investigations Laboratory tests	CSF (OCBs)	EMG/ NCS	MRI Brain	c-spine	MEPs
1 (LB)	F	69	18	Bilateral foot drop Progressive LL and UL weakness Symptomatic fasciculations	IHD ↑BP	Clopidogrel Atenolol BFMTZ ISMN Lisinopril, Riluzole	Nil	NAD	Anti-GM1 Ab and anti-MAG Ab negative, CK 328, UPEP normal	NAD (absent)	AHD (UL and LL) SNAPs/SNCVs normal	NAD	NAD	NAD
2 (HR)	F	67	24	Bilateral foot drop Progressive LL and UL weakness Symptomatic fasciculations	Non-toxic goitre	Ranitidine Lofepramine Riluzole	Nil	NAD	Anti-GM1 Ab and anti-MAG Ab negative, CK normal, UPEP normal	NAD (absent)	AHD (UL and LL) SNAPs/SNCVs Normal	NAD	NAD	NAD
3 (GH)	M	61	10	Progressive LL weakness and cramps	Nil	Riluzole	Nil	NAD	Anti-GM1 Ab and anti-MAG Ab negative, CK 372, UPEP normal, AR mutations negative	NAD (absent)	AHD (UL and LL) SNAPs/SNCVs Normal	NAD	MRI lumbar spine moderate canal stenosis (L3/4 and L4/5) without neural compression	NAD
4 (JD)	M	73	12	Weakness R UL initially, progressing to bilateral UL and LL weakness with bulbar involvement	Cervical spondylosis IHD (MI 2001) CD Eczema Rhinitis Appendectomy RIH	Mesalazine Aspirin Ramipril Atenolol Riluzole	Nil	NAD	Anti-GM1 Ab and anti-MAG Ab negative, CK normal, IgG lambda paraprotein (immuno-fixation), UPEP normal	NAD (absent)	AHD (UL and LL) SNAPs/SNCVs Normal	NAD	MRI cervical spine posterior disc osteophytes with C3/C4 and C6/ C7 stenosis and ligamentous hypertrophy but no root or cord compression	NAD
5 (PS)	M	65	60	Generalized cramps and fasciculations (legs, arms and abdomen) for 5 years and left foot drop for 12 months	IHD ↑BP	Atenolol ISMN Aspirin Amlodipine GTN Simvastatin, Riluzole	Nil	NAD	Normal B12, autoimmune screen, SPEP, IgG, IgA, IgM, CK 249	NAD (absent)	AHD (UL and LL) SNAPs/SNCVs Normal	NAD	NAD	NAD
6 (KM)	M	65	>60	Progressive LL weakness and mild bilateral foot drop. Some UL weakness on examination	↑BP Peptic ulcers	Bendroflumethiazide, Glucosamine, Chondroitin, Esomeprazole	Nil	NAD	Anti-GM1 Ab and anti-MAG Ab negative, CK 450, SPEP ↑gamma-band	NAD (absent)	AHD (UL and LL) SNAPs/SNCVs Normal	NAD	Mild degenerative changes in lumbar spine	Low threshold

Ab = antibody; AHD = anterior horn cell disease; AR = androgen receptor; BFMTZ = bendroflumethiazide; ↑BP = hypertension; CD = Crohn's disease; CK = creatine kinase; HPC = history of presenting complaint; IHD = ischaemic heart disease; ISMN = isosorbide mononitrate; L = left; LL = lower limb; MEPs = motor-evoked potentials; MI = myocardial infarction; NAD = no abnormality detected; NCS = nerve conduction studies; OCBs = oligoclonal bands; R = right; RIH = right inguinal herniorrhaphy; SEPs = somatosensory-evoked potentials; SNAP = sensory nerve action potential; SNCV = sensory nerve conduction velocity; SPEP = serum protein electrophoresis; UL = upper limb; UPEP = urine protein electrophoresis.

in all muscles. In some patients, the threshold was either very high or could not be determined; here, magnetic stimulation at the maximum stimulator output was used. A steady background contraction was maintained throughout the recording period.

Precision grip task

To test intermuscular coherence, subjects were asked to perform a simple repetitive task. For the upper limb, they were required to perform a precision grip, guided by a length of compliant plastic tubing (Portex; external diameter 10 mm, internal diameter 8 mm, 19-cm long) attached to the index finger and thumb with micropore tape. Subjects were instructed to oppose the two ends of the tubing, a movement that required a minimum force of 1 N. The task followed the pattern of a 3-s contraction, followed by a 2-s rest period; auditory cues to instruct the subject when to grip and relax were generated by a computer. This is an 'auxotonic' task (from the Greek 'auxein' to increase and 'tonos' tension), as force varies with displacement in a spring-like fashion. The task is similar to that used in our previous work, although without measurement of digit displacement (Kilner *et al.*, 2000; Baker and Baker, 2003; Riddle *et al.*, 2004). For lower limb investigations, subjects were asked to dorsiflex the ankle in air; once again, computer-generated tones cued the onset and offset of contractions. For each task, subjects were asked to perform 100 movement repetitions. If necessary, this was divided into a number of different recordings, separated by rests to prevent fatigue (only required for one patient).

Animal recording

To complement the measurements made in patients, we also performed motor-evoked potentials and intermuscular coherence in a single female macaque monkey (*Macaca mulatta*) that had been subjected 3 months previously to a unilateral lesion of the pyramidal tract at the medulla. The lesion was made by a radiofrequency thermocoagulation probe stereotaxically introduced into the pyramid while the animal was under general anaesthesia. EMG recordings were made using implanted electrodes (Miller *et al.*, 1993) or surface electrodes placed on the skin overlying muscles. Motor-evoked potentials were recorded whilst the animal was lightly sedated with ketamine (10 mg/ kg intramuscularly) and used a small figure-of-eight coil (loop diameter 25 mm). Intermuscular coherence was recorded in the conscious animal during performance of a simple task. This required the end of a spring-loaded rod to be grasped and pulled towards the animal; release of the rod then led to a food reward. *Post hoc* trials were selected to include only those with a hold period longer than 1.64 s. Analysis of intermuscular coherence then proceeded as for the patient recordings, using only EMG data from the hold phase of the task. The task was performed with both the affected and unaffected upper limb in turn, allowing comparison of intermuscular coherence between sides contralateral and ipsilateral to the pyramidal tract lesion.

All surgical procedures were carried out under aseptic conditions and general anaesthesia (3%–5% sevofluorane inhalation in 100% O_2 with alfentanil infusion), with a full programme of postoperative analgesics [buprenorphine (Vetergesic®) 10 mg/kg, Reckitt and Colman Products; carprofen (Rimadyl®) 5 mg/kg, Pfizer] and antibiotics (LA Clamoxyl 15 mg/kg). All animal procedures were covered by appropriate licences from the UK Home Office and were approved by the Ethical Review Committee of Newcastle University.

Analysis

Data analysis was performed using custom-written Matlab (Mathworks Inc.) routines and followed the procedures used in our previous publications (Baker and Baker, 2003; Riddle *et al.*, 2004). Analysis focused on the central 1.64-s of the 3-s hold period, as beta frequency oscillations are greatest during periods of steady contraction. EMG power spectra and intermuscular coherence were calculated using two contiguous 0.82-s long sections of data from each trial and a 4096-point Fast Fourier Transform (Baker *et al.*, 1997). This yielded a frequency resolution of 1.22 Hz. EMG signals were full-wave rectified before Fourier transforms were calculated. Significance levels were calculated using the method described in Rosenberg *et al.* (1989), which takes account of the length of the recording to estimate the expected variation in coherence under the null hypothesis that there is no coupling between the two signals. Intermuscular coherence was calculated between the first dorsal interosseous muscle and both flexor digitorum superficialis and extensor digitorum communis muscles in the upper limb and between extensor digitorum brevis and both tibialis anterior and gastrocnemius-soleus in the lower limb. By confining our analysis to these muscle pairs, which are physically well separated, we avoided a contribution of electrical cross-talk to the measured intermuscular coherence (Kilner *et al.*, 2002).

Intermuscular coherence values are reported in two ways. First, we averaged spectra for a given muscle pair across all patients within a group, providing a visual representation of the dependence of coherence on frequency. Significance limits for these averaged spectra were computed as described in Evans and Baker (2003); this method adjusts the limits on the individual spectra to reflect the improved confidence achieved in averaging multiple independent measures. Second, we calculated the mean coherence across the beta frequency band (15–30 Hz) for a given muscle pair in single subjects. This allowed us to estimate the probability distribution of mean beta-band coherence across the population. Experimental distributions were fitted to a log-normal curve; the appropriateness of this fit was assessed using a Kolmogorov-Smirnov test. Using these fitted curves, we were able to determine a likelihood ratio curve, which estimated the relative likelihood that intermuscular coherence of a given value came from the primary lateral sclerosis or healthy control groups.

As well as a magnitude, coherence analysis can yield phase values, indicating the average phase difference between the two signals. To measure meaningful phases, significant coherence at that frequency must be present. Because our major finding was a lack of coherence after corticospinal tract degeneration, we were unable to assess phase in those patients, and coherence phase is therefore not considered further in this article.

Results

Figure 1 shows the results of investigations in a single patient with primary lateral sclerosis (Patient AB) followed longitudinally over a 2-year period. Patient AB presented at the age of 64 years with a 2-year history of progressive tetraparesis. This began in the lower limbs and gradually ascended; the left arm and leg were more severely affected than the right, and the investigations were thus limited to this side. Patient AB had no lower motor neuron signs and normal nerve conduction studies. During the initial investigation (Fig. 1A), motor-evoked potentials were small, delayed and poorly formed. Intermuscular coherence in the beta-band was present (Fig. 1C), although for first dorsal interosseous-flexor
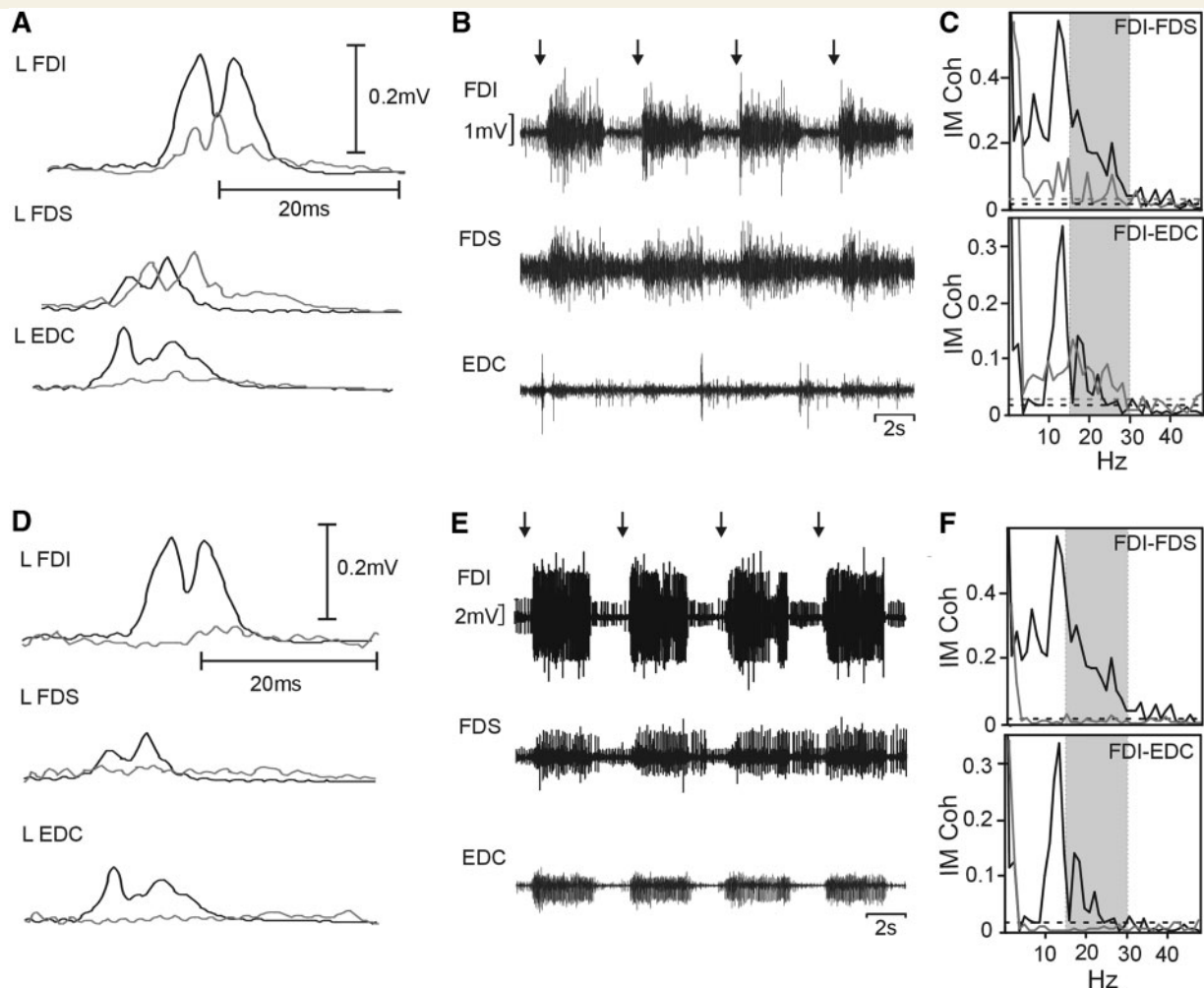
Figure 1 (**A–C**) Results obtained from Patient AB on her first assessment in the laboratory. (**A**) Motor-evoked potentials are shown from three muscles in Patient AB (grey) and an age-matched control subject (black). (**B**) Raw EMG records show modulation with the task; arrows indicate trial onset. (**C**) Intermuscular coherence spectra. Grey boxes indicate the frequency window of interest, and significance levels are represented by grey (Patient AB) and black (control) dashed lines. Note the higher significance level for Patient AB who completed fewer trials (these data were not used in the average to reduce coherence bias). (**D–F**) As in **A–C**, data from the patient's second visit to the laboratory. EDC = extensor digitorum communis; FDI = first dorsal interosseous; FDS = flexor digitorum superficialis; IM Coh = intermuscular coherence.

digitorum superficialis, it was smaller than the illustrated age-matched control subject (black trace). The patient was reassessed 22 months later, during which time the disease had gradually progressed. There was particular deterioration in mobility as a result of lower limb weakness, and the arms were notably weaker. At this point, there were no motor-evoked potentials present, even when the stimulator output was maximal (Fig. 1D). There was no significant intermuscular coherence in any of the muscles tested (Fig. 1F). As such, it appears that both magnetic brain stimulation and coherence are measures that reflect the degeneration of the corticospinal tract.

A further test of the ability of intermuscular coherence to detect corticospinal tract damage was carried out in a macaque monkey, which had undergone a unilateral surgical lesion of the pyramidal tract as part of an unrelated study in our laboratory. Post-mortem, a transverse section through the pyramids at the level of the

medulla showed the extent of the lesion, and that it was confined to the left pyramidal tract (Fig. 2A). Motor-evoked potentials could only be elicited in the left muscles; no motor-evoked potentials were seen on the right side, which was contralateral to the lesioned pyramid (Fig. 2B). Intermuscular coherence between coactivated muscles on the left side was clearly above significance at beta frequencies (Fig. 2C; grey shading). On the right side, there was significant intermuscular coherence at lower frequencies, probably reflecting a broad timescale correlation in the timing of activation in these muscles (this was also apparent on the left side). However, intermuscular coherence in the beta frequency band was close to the significance limit.

Intermuscular coherence spectra between different muscle pairs are shown for the patient subgroups and healthy control subjects in Figs 3 and 4. These results have been averaged across all patients within a particular group; the significance limits shown on
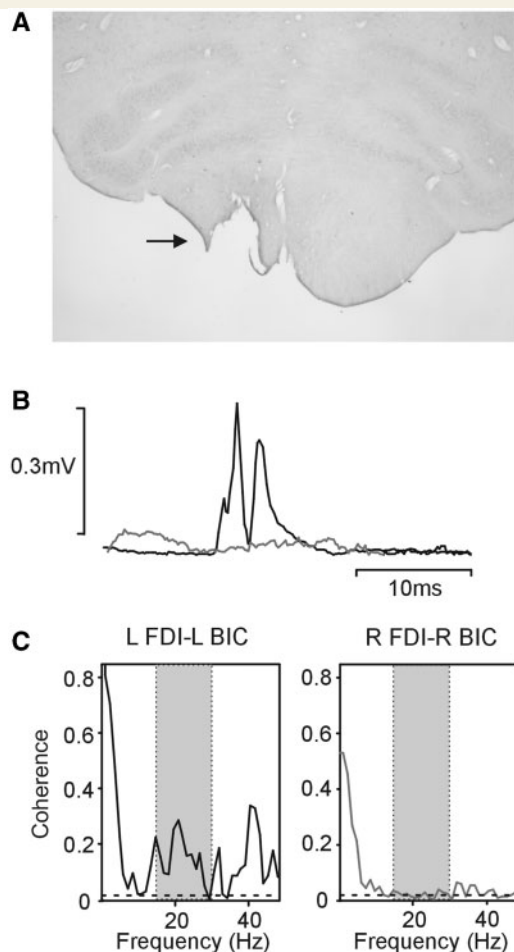
Figure 2 (**A**) Transverse section through the pyramids at the level of the medulla showing the extent of the pyramidal tract lesion in monkey M. (**B**) Motor-evoked potentials obtained from left (black) and right (grey) first dorsal interosseous muscles 3 months post lesion to the left pyramidal tract. (**C**) Intermuscular coherence plots calculated from EMG data collected during a steady hold task. Dashed line indicates significance level. BIC = ; FDI = first dorsal interosseous; L = left; R = right.

these graphs as dashed lines are calculated taking into account the improvement of signal:noise ratio yielded by averaging in this way [see Evans and Baker (2003) for details of the method]. In all muscle pairs, both in the upper and lower limbs, average intermuscular coherence was below significance for patients with primary lateral sclerosis (Fig. 3). This suggests a remarkably robust result, because even low levels of intermuscular coherence would be detected by averaging in this way across patients. By contrast, average coherence rose above significance for all muscle pairs examined for the patients with progressive muscular atrophy (Fig. 4).

Averaging coherence across patient groups provides a good summary of the impact of a given disease process on intermuscular coherence. However, to be useful as a diagnostic measure, it is necessary that results in individual patients are sufficiently robust to detect an abnormality. We accordingly measured the average intermuscular coherence over the beta-band in individual patients.

The distribution of these mean intermuscular coherence values in different patient groups is shown as cumulative probability curves in Fig. 5A–D. Results are shown for the four different muscle pairs. Significant differences were found in all muscle pairs between patients with primary lateral sclerosis and control subjects (first dorsal interosseous-flexor digitorum superficialis: $P < 0.005$; first dorsal interosseous-extensor digitorum communis: $P < 0.05$; extensor digitorum brevis–tibialis anterior and extensor digitorum brevis–gastrocnemius/soleus: $P < 0.001$; t-test) but not between progressive muscular atrophy patients and controls ($P > 0.1$, t-test).

Overlain on the experimental cumulative distribution plots of Fig. 5A–D are curves derived from the normal distribution of log-transformed coherence, with the mean and standard deviation derived from the experimental data. In all cases, the distributions did not significantly deviate from log-normal ($P > 0.4$, Kolmogorov-Smirnov test). Table 3 lists the parameters of these fitted distributions.

The fitted normal probability distributions of Fig. 5A–D have also been used to calculate likelihood ratios (odds ratios) plotted underneath. This allows us to read off the relative likelihood that a given value of mean beta-band intermuscular coherence has come from the primary lateral sclerosis or the control population. As an example, the vertical lines on each plot mark the mean coherence values determined from the patient previously illustrated in Fig. 1. We see that a mean beta-band intermuscular coherence of 0.0084 in the first dorsal interosseous-flexor digitorum superficialis muscle pair is 6.8 times more likely to come from a patient with primary lateral sclerosis than a control subject. Corresponding ratios for the other muscle pairs for this patient were as follows: first dorsal interosseous-extensor digitorum communis, 3.6; extensor digitorum brevis–tibialis anterior, 9.9; extensor digitorum brevis–gastrocnemius/soleus, 3.7.

Note that these likelihood ratios depend heavily on the form of the probability density used to fit the experimental distributions. It is in the tails of the distributions that the fit between experimental and normal curves is likely to be most divergent; accordingly, likelihood ratio curves have only been shown over the range of mean beta-band intermuscular coherence values encountered in our experimental data set.

The likelihood ratio curves of Fig. 5A–D clearly could provide useful information, but even at their peak (around 10:1), the ratios are not high enough to yield a definitive diagnosis. However, because the measurements from each muscle pair are statistically independent, a combined likelihood ratio can be computed by multiplying together the values from the different muscle pairs. In the illustrated patient with primary lateral sclerosis, taking the product of the ratios from all four muscles, we would conclude that this patient was 880 times more likely to have a degenerated than normal corticospinal tract.

Prospective case study

Figure 6 summarizes the results obtained from a separate patient studied prospectively after presentation to the motor neuron disease clinic. Patient AP is a 30-year-old male with a 2-year history of progressive weakness and muscle wasting in the lower limbs. He initially presented with a unilateral foot drop; symptoms then
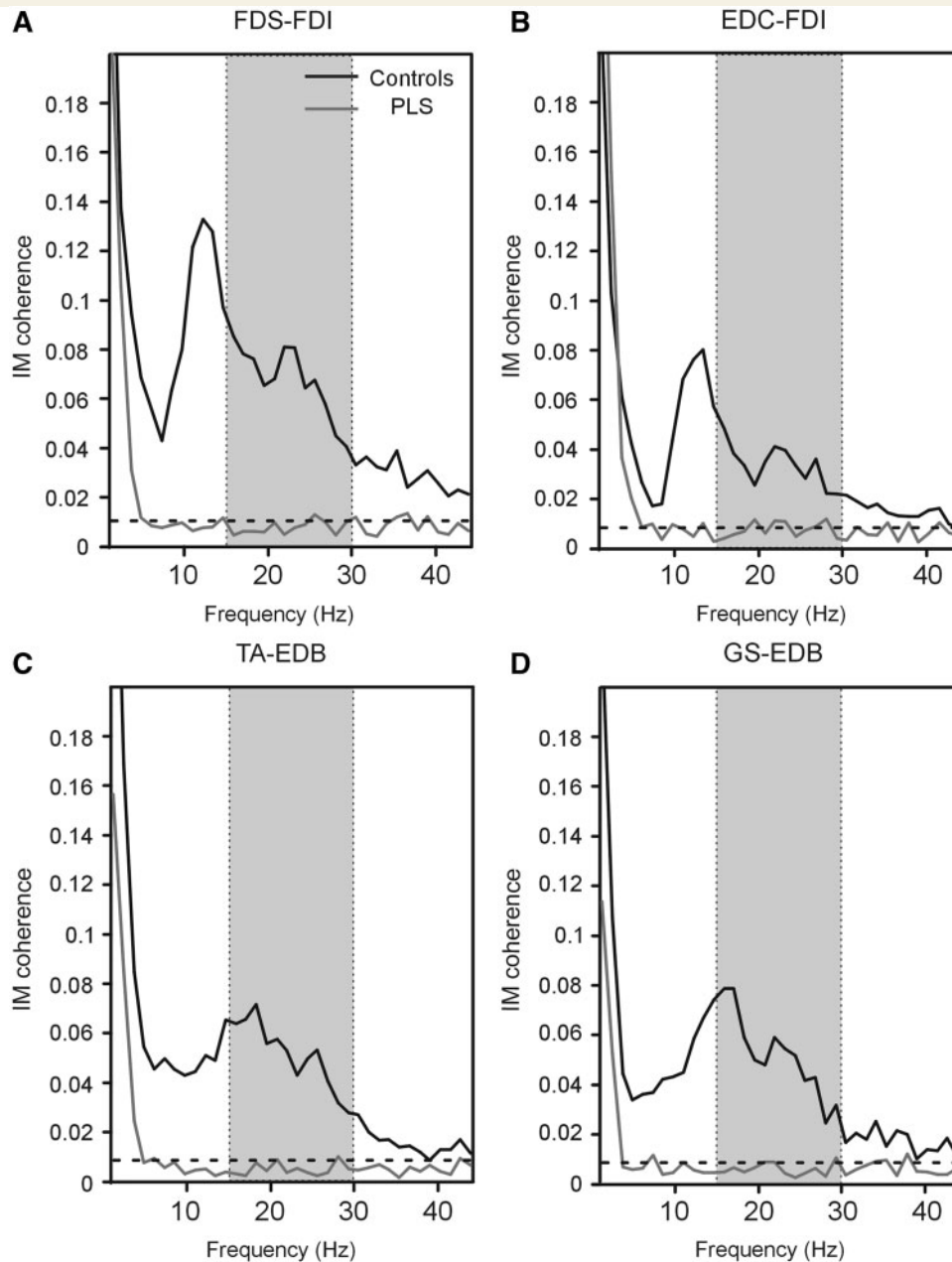
Figure 3 Population averages are shown for intermuscular coherence in primary lateral sclerosis patients (grey) and age-matched controls (black). Upper limb results are shown in **A–B** [eight patients (15 muscles) & 16 controls (32 muscles)] and lower limb results are shown in **C–D** [six patients (12 muscles) & 12 controls (24 muscles)]. Grey shaded boxes indicate the frequency window of interest. EDB = extensor digitorum brevis; EDC = extensor digitorum communis; FDI = first dorsal interosseous; FDS = flexor digitorum superficialis; GS = gastrocnemius/soleus; IM = intermuscular; PLS = primary lateral sclerosis; TA = tibialis anterior.

progressed in an ascending and asymmetric manner predominantly affecting the left leg. There was no upper limb involvement and no upper motor neuron signs at this stage. Initial EMG studies revealed neurogenic changes that were confined to the lower limbs (concentric needle EMG demonstrated unstable polyphasic motor units, positive sharp waves and fibrillation potentials in right and left tibialis anterior, medial gastrocnemius and vastus lateralis and right abductor hallucis) in the presence of normal sensory nerve action potentials and sensory nerve conduction velocities. This was felt to be consistent with a lumbo-sacral

polyradiculopathy. A follow-up study was completed 10 months later because there was a clear progression in symptoms; the lower limb muscles became progressively more wasted and the patient became aware of fasciculations in the lower limbs. The second neurophysiological examination revealed severe active neurogenic changes in the lower limbs combined with mild changes in the upper limbs (i.e. no spontaneous activity or unstable motor units). These were thought to be indicative of diffuse anterior horn cell disease. However, because clinical evidence of upper motor neuron involvement was restricted to the
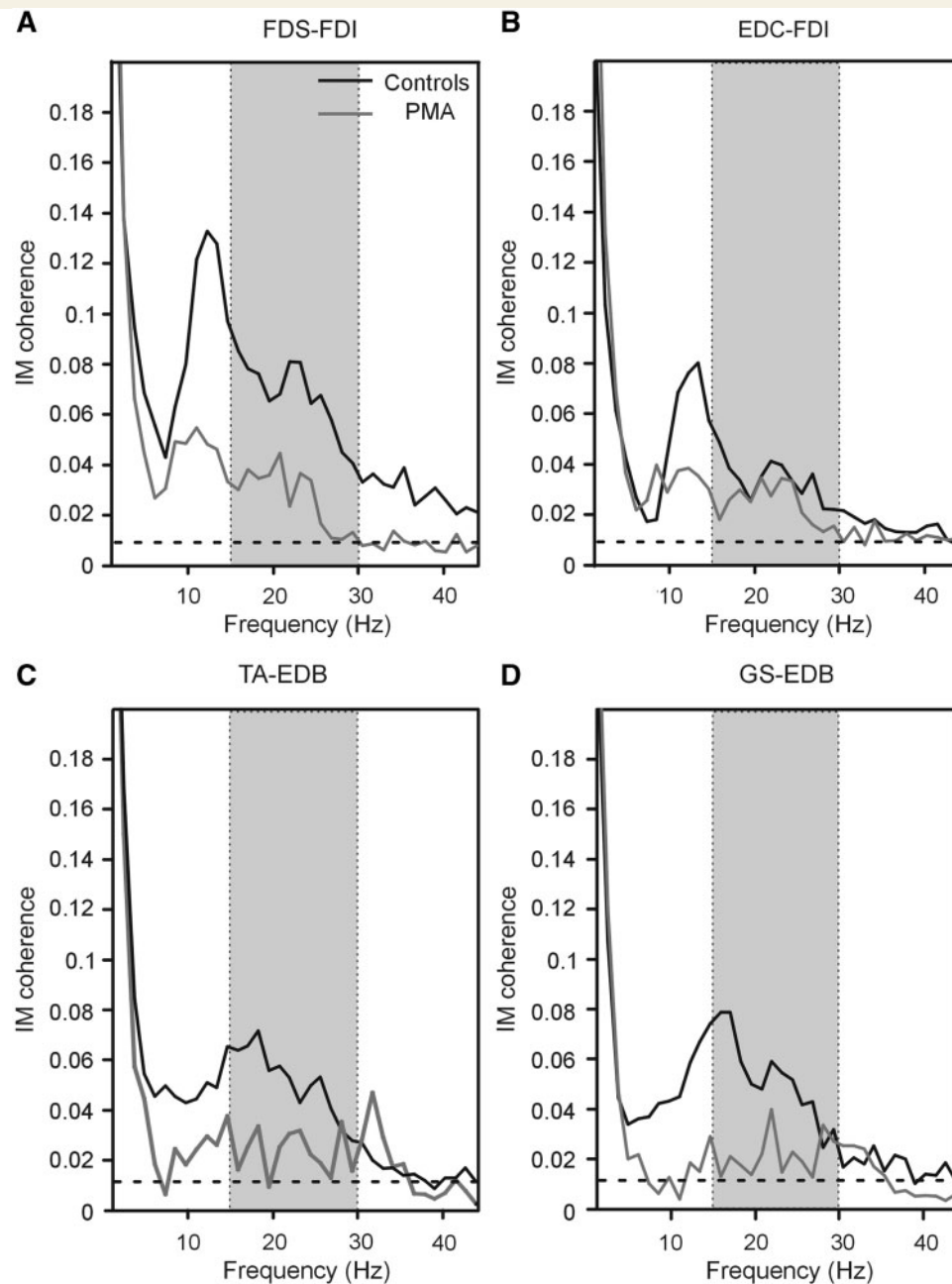
Figure 4 Population averages are shown for intermuscular coherence in patients with progressive muscular atrophy (grey) and age-matched control subjects (black). Upper limb results are shown in (**A**) (six patients, 10 muscles) and (**B**) (16 control subjects, 32 muscles), and lower limb results are shown in (**C** and **D**) [six patients and 13 control subjects (24 muscles)]. Grey shaded boxes indicate the frequency window of interest. EDB = extensor digitorum brevis; EDC = extensor digitorum communis; FDI = first dorsal interosseous; FDS = flexor digitorum superficialis; GS = gastrocnemius/soleus; IM = intermuscular; PMA = progressive muscular atrophy; TA = tibialis anterior.

lower limbs, the patient only met diagnostic criteria for clinically possible motor neuron disease. At this stage, no significant beta-band intermuscular coherence was found in either the lower or upper limb (Fig. 6B). Subsequently, genetic tests revealed this patient to have a point mutation at c341T>C in the *SOD1* (superoxide dismutase) gene on chromosome 21q. This mutation has been shown to be linked to familial amyotrophic lateral sclerosis (Rosen *et al.*, 1993). Based on the curves of Fig. 5A–D, the combined likelihood ratio for this patient having a degenerated

versus a normal corticospinal tract across all muscle pairs was calculated as 281:1 (first dorsal interosseous-flexor digitorum superficialis: 7.95; first dorsal interosseous-extensor digitorum communis: 5.9; extensor digitorum brevis–tibialis anterior: 0.54; extensor digitorum brevis–gastrocnemius/soleus: 11.04).

Detection of abnormal intermuscular coherence was completed ~6 months before the positive genetic test for Patient AP. It is likely that these changes in intermuscular coherence actually occurred earlier in the disease course but we were unable to
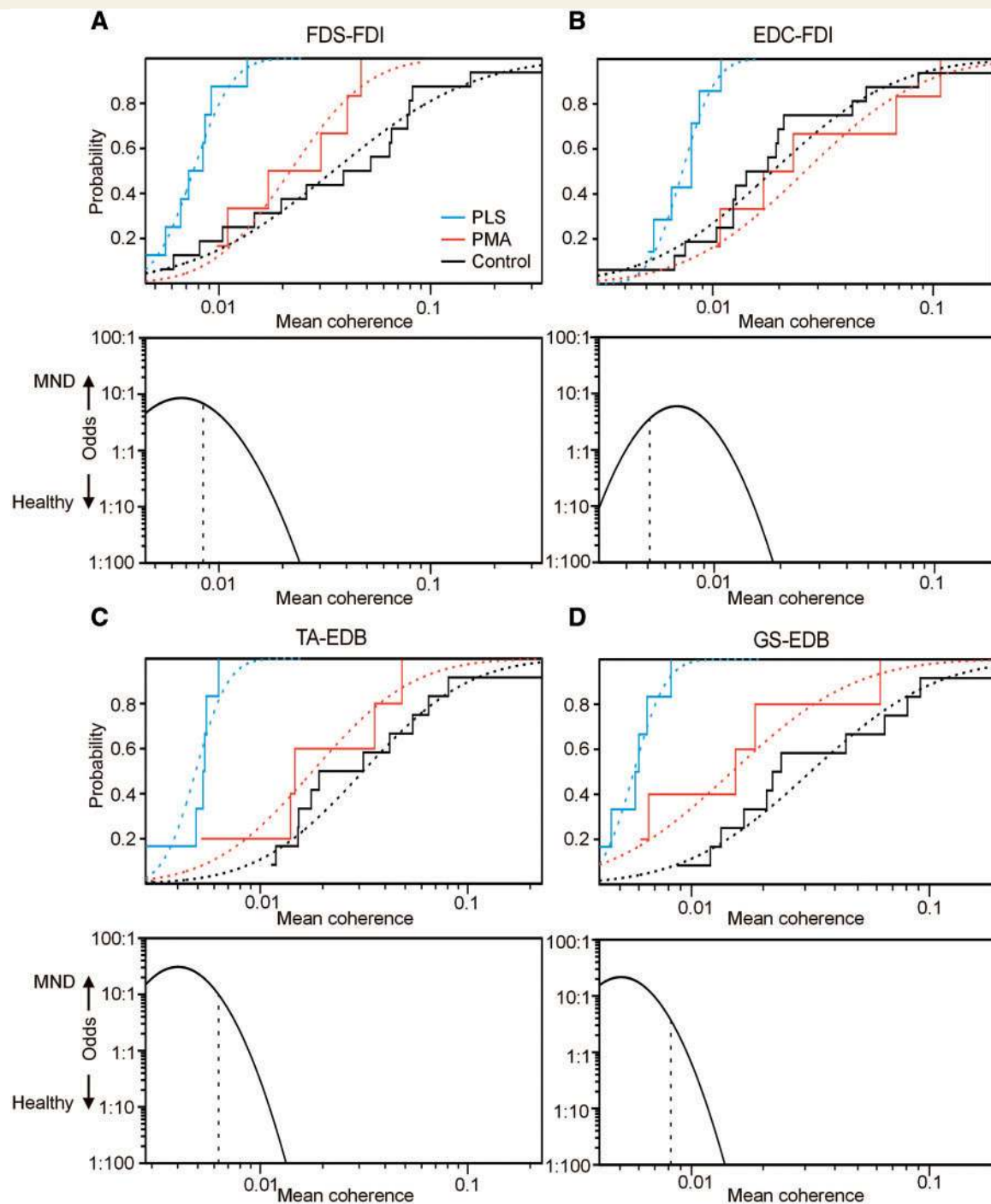
Figure 5 Cumulative distribution plots are shown for intermuscular coherence between (**A**) first dorsal interosseous-flexor digitorum superficialis (FDI-FDS); (**B**) first dorsal interosseous-extensor digitorum communis (FDI-EDC); (**C**) extensor digitorum brevis–tibialis anterior (EDB-TA); and (**D**) extensor digitorum brevis–gastrocnemius/soleus (EDB-GS). Coherence is plotted on a logarithmic scale. In each case, the individual histograms of coherence values are shown for patients with primary lateral sclerosis (blue), progressive muscular atrophy (red) and control subjects (black) with the log-normal curve fit (dotted line) superimposed. The odds ratio curve is also displayed for each muscle pair. MND = motor neuron disease.

confirm this because the patient was only referred for motor-evoked potentials or intermuscular coherence once there was a strong clinical suspicion of motor neuron disease.

Since the genetic diagnosis, Patient AP's condition has progressed resulting in wasting and weakness in both hands. He

now relies on two crutches for day-to-day ambulation with intermittent use of a wheelchair. This progressive disability has prompted his recent move into a specially adapted bungalow. Despite the clear progression in symptoms, Patient AP would remain classified as 'clinically possible' motor neuron disease on

Table 3 Parameters of log-normal fits to experimental distributions of beta-band intermuscular coherence

Muscle pair	Control	PLS	PMA
FDI-FDS			
Mean	−1.459	−2.121	−1.663
SD	0.522	0.146	0.291
FDI-EDC			
Mean	−1.728	−2.138	−1.582
SD	0.441	0.118	0.424
EDB-TA			
Mean	−1.504	−2.311	−1.747
SD	0.400	0.124	0.381
EDB-GS			
Mean	−1.500	−2.243	−1.830
SD	0.415	0.108	0.409

Coherence values were first averaged over the 15–30 Hz band and then transformed by taking $\log_{10}$. The table lists the mean and standard deviation of these log-transformed beta-band intermuscular coherence values, which were used to generate the curves overlain on the experimental distributions of Fig. 5.
EDC = extensor digitorum communis; FDI = first dorsal interosseous; FDS = flexor digitorum superficialis; GS = gastrocnemius/soleus; PLS = primary lateral sclerosis; PMA = progressive muscular atrophy; TA = tibialis anterior.

standard criteria if the positive genetic findings were disregarded. The addition of intermuscular coherence to the Awaji criteria would have permitted a classification of 'clinically probable' motor neuron disease, the qualifying criterion for riluzole therapy within the UK National Health Service and the typical threshold for entry to most therapeutic trials, and would have advanced the diagnosis in this patient by almost 2 years (Fig. 6A).

Discussion

Beta-band oscillations in muscle activity are thought to occur as a result of a common cortical drive from the corticospinal tract. Various hypotheses on their function suggest that they could be used for sensorimotor processing or calibration (Baker, 2007) or promote stable motor output (Pogosyan *et al.*, 2009). These oscillations and the coupling between them disappear after stroke and complete spinal cord injury in patients (Farmer *et al.*, 1993; Norton *et al.*, 2003, 2004; Hansen *et al.*, 2005) and following unilateral lesions of the corticospinal tract (at the level of the spinal cord) in monkeys (Nishimura *et al.*, 2009; Nishimura and Isa, 2011). Beta-band oscillations have also been demonstrated to reflect recovery of function in patients with partial spinal cord injury (Norton and Gorassini, 2006). In support of these findings, we observed no significant beta-band intermuscular coherence in a monkey with a focal lesion of the corticospinal tract, or in patients with primary lateral sclerosis. Histological evidence from post-mortem studies has confirmed that neuronal attrition is limited to the Betz cells within layer V of primary motor cortex in primary lateral sclerosis (Pringle *et al.*, 1992). This would suggest that it is specifically the large diameter fastest conducting corticospinal axons that are fundamental to beta-band intermuscular coherence in man.

Roopun *et al.* (2006) showed evidence of beta oscillations (20–30 Hz) generated in layer V pyramidal cells in cortical slices. These oscillations were not dependent on synaptic input but were abolished by reducing gap junction conductance between the pyramidal cells within layer V. Jackson *et al.* (2002) demonstrated that the phase of beta oscillations could be reset by stimulation of the pyramidal tract in monkeys. Baker *et al.* (2003) showed that motor cortical oscillations were encoded by pyramidal tract neurons. These reports all support the suggestion that pyramidal tract neurons are involved in the generation of beta oscillations and their propagation to the periphery.

Beta-band intermuscular coherence was observed in all control subjects tested, including age-matched healthy subjects and patients with progressive muscular atrophy. We 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. We therefore propose that assessment of intermuscular coherence could provide additional diagnostic information about involvement of the corticospinal tract in motor neuron disease. As illustrated by the case study, intermuscular coherence can be absent before clinical criteria for motor neuron disease are met (Fig. 6). The additional information provided by intermuscular coherence studies might therefore also allow the definitive diagnosis of motor neuron disease to be made earlier in the course of the disease, with obvious implications for therapy and recruitment to clinical trials. Previous studies have shown that the presence of corticomuscular coherence in a given healthy individual is repeatable across different measurement sessions (Pohja *et al.*, 2005; Witham *et al.*, 2011), and in our experience, intermuscular coherence is even more reliable. This should therefore be a robust and reliable test.

In an earlier monkey study, animals recovering from a corticospinal tract lesion in the high cervical spinal cord lost beta-band intermuscular coherence, but progressively developed intermuscular coherence at higher (gamma-band) frequencies (Nishimura *et al.*, 2009). Nishimura *et al.* (2009) proposed that gamma-band intermuscular coherence reflected a subcortical network involved in functional recovery after the lesion. The lack of such gamma-band coupling in our patients with primary lateral sclerosis (Fig. 3) suggests that this compensation process—whatever its origin—does not occur during the progressive loss of corticospinal axons seen in motor neuron disease.

Patient characteristics

Although the diagnosis of clinically proven primary lateral sclerosis can only be made at post-mortem, all the patients included in this study fulfilled the criteria for clinically definite primary lateral sclerosis (Pringle *et al.*, 1992). Recently an upper motor neuron dominant amyotrophic lateral sclerosis variant has been recognized (Gordon *et al.*, 2006). Although this group have a better prognosis than most patients with amyotrophic lateral sclerosis (average life expectancy 6–7 years from diagnosis), their prognosis is significantly worse than that of patients with primary lateral sclerosis. Upper motor neuron dominant patients develop evidence of active denervation on EMG 3–4 years after presenting with upper motor neuron signs, and therefore, it has been suggested that the
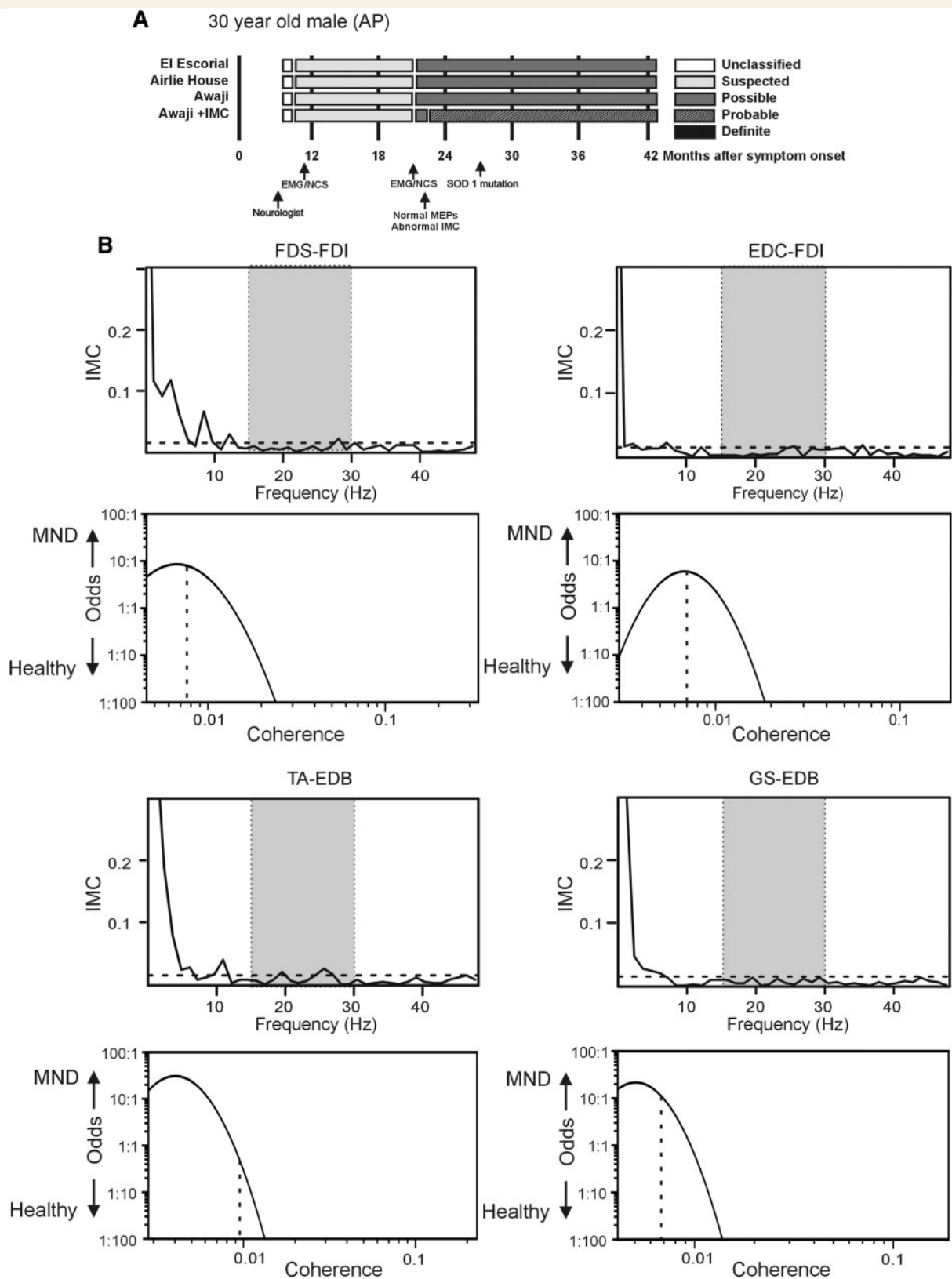
Figure 6 Prospective patient data from a 30-year-old male patient with suspected anterior horn cell disease. (**A**) Gantt chart showing timeline of diagnosis according to available consensus criteria (not considering coherence or genetic tests) and clinical tests. (**B**) Intermuscular coherence spectra for each muscle pair are illustrated. The shaded box indicates the frequency window of interest. Underneath each frequency spectrum is the corresponding odds ratio plot from Fig. 5. Dashed line shows log coherence values found in the left upper and lower limbs for Patient AP. EDB = extensor digitorum brevis; EDC = extensor digitorum communis; EMG/NCS = electromyogram/nerve conduction studies; FDI = first dorsal interosseous; FDS = flexor digitorum superficialis; GS = gastrocnemius/soleus; IMC = intermuscular coherence; MEPs = motor-evoked potentials; MND = motor neuron disease; TA = tibialis anterior.

diagnostic criteria for primary lateral sclerosis should be modified to stipulate that EMGs must be normal 4 years (rather than 3 years) after onset (Gordon *et al*., 2006). Although the diagnosis of primary lateral sclerosis in one patient could potentially be revised to upper motor neuron dominant amyotrophic lateral sclerosis on this criterion, this change would not affect our findings for two important reasons. First, the predominant histological picture in upper motor neuron dominant amyotrophic lateral sclerosis, particularly in the first 3 to 4 years, is one of corticospinal tract destruction. Second, 15–30 Hz intermuscular coherence persists despite the widespread anterior horn cell destruction observed in patients with progressive muscular atrophy.

Four patients with primary lateral sclerosis in our study were taking the neuroprotective agent riluzole (Table 1), which has a number of potentially confounding pharmacological actions. Riluzole blocks non-inactivating persistent-inward sodium current (Urbani and Belluzzi, 2000), activates TREK-1 and TRAAK leak potassium conductances (Duprat *et al*., 2000) and blocks protein kinase C (Noh *et al*., 2000), thereby reducing glutamate release (Wang *et al*., 2004), increasing glutamate reuptake (Fumagalli *et al*., 2008) and enhancing the postsynaptic effects of GABA(A)-mediated inhibition (He *et al*., 2004). Reduced extracellular glutamate concentrations are unlikely to affect beta frequency oscillations in frontal cortex (Roopun *et al*., 2006), whereas enhanced GABA(A) transmission may modulate oscillations in 8–12 and 15–30 Hz ranges (Baker and Baker, 2003). Although by blocking protein kinase C riluzole could theoretically inhibit intracellular calcium oscillations (Kim *et al*., 2005), there is no evidence linking <0.01 Hz intracellular calcium fluctuations and 8–30 Hz cortical oscillations. Reassuringly, in our study, there was no significant difference between the results obtained from the four patients with primary lateral sclerosis who were taking riluzole and the four who were not. Moreover, the patients with progressive muscular atrophy who were taking riluzole (Table 2) all had normal intermuscular coherence.

Corticospinal tract degeneration has been demonstrated in a small group of patients with progressive muscular atrophy at post-mortem (Ince *et al*., 2003). It is impossible to determine at what stage of the disease these features manifest, although a recent tract imaging study showed there is no difference in corticospinal tract integrity between patients with progressive muscular atrophy and control subjects (Cosottini *et al*., 2005). Whilst we cannot prove that there was no upper motor neuron involvement in any of our patients with progressive muscular atrophy, they all had coherence in the beta range, which suggests that this was not a primary feature of their disease.

Clinical applications of coherence analysis

Recently it has become clear that sensory afferents also play an important role in 15–30 Hz corticomuscular coherence (Baker *et al*., 2006; Riddle and Baker, 2006; Witham *et al*., 2010, 2011) and intermuscular coherence (Pohja and Salenius, 2003; Kilner *et al*., 2004). There are also reports that central sensory pathways can be implicated in motor neuron disease (Hamada

et al., 2007; Mochizuki *et al*., 2011). Therefore, any diagnostic inference regarding corticospinal tract function using intermuscular coherence can only be made in the presence of normal somatosensory-evoked potentials, sensory nerve action potentials and sensory nerve conduction velocities. Such tests were performed in our patients with primary lateral sclerosis, yielding normal findings. By contrast, where normal intermuscular coherence is detected, corticospinal tract degeneration is unlikely. In such cases, it is unnecessary also to test electrophysiologically for intact sensory pathways; following this logic, somatosensory-evoked potentials were not measured in our patients with progressive muscular atrophy.

Beta-band intermuscular or corticomuscular coherence also seems to require functioning basal ganglia circuitry (Grosse *et al*., 2002) because in Parkinson's disease it is diminished when treatment is withdrawn and restored to levels comparable to those seen in healthy age-matched control subjects by stimulation of the subthalamic nucleus or administration of L-DOPA (McAuley *et al*., 2001; McKeown *et al*., 2006). Although Parkinson's disease and motor neuron disease occur together very infrequently (Williams *et al*., 1995), caution should be exercised when interpreting results if parkinsonian features are present.

This study was designed to provide some clarification of the origin of coherence and its potential value as a diagnostic indicator. Our results demonstrate that intermuscular coherence is a simple, inexpensive and accessible measure of corticospinal tract integrity. All that is required are facilities for EMG recording (available in all Clinical Neurophysiology departments) and the requisite analysis software. A large prospective clinical trial is clearly warranted to further examine the potential impact of this technique on diagnosis.

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