Double cortical stimulation in amyotrophic lateral sclerosis

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Abstract

Objective—**Transcranial double magnetic stimulation on the motor cortex was used to investigate central motor tract function in 16 patients with amyotrophic lateral sclerosis, five with spinal muscular atrophy, and 16 age matched normal controls.** ***Methods***—**Surface EMG responses were recorded from the relaxed abductor pollicis brevis (APB) muscle.**
Results—**Responses to test stimuli were markedly attenuated by a subthreshold conditioning stimulus given at a condition-test (C-T) interval of 1–4 ms in normal controls and patients with spinal muscular atrophy, but attenuation was mild in patients with amyotrophic lateral sclerosis. In the normal controls this suppression was caused by activation of the intracortical inhibitory mechanism because responses to electrical test stimuli and the H wave were not suppressed by the same magnetic subthreshold conditioning stimulus. In amyotrophic lateral sclerosis the effect of the conditioning cortical stimulus on the H wave was also in the normal range.**
Conclusion—**The intracortical inhibitory mechanism may be impaired in patients with amyotrophic lateral sclerosis.**

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Keywords: motor evoked potential; magnetic stimulation; amyotrophic lateral sclerosis; double cortical stimulation

The pathogenesis of amyotrophic lateral sclerosis has been an enigma for over a century. A recent hypothesis suggests that the corticomotor neuronal pathways are abnormally excitable in the early stage of amyotrophic lateral sclerosis.[1][2] Eisen[3] showed that the cortical threshold for producing motor evoked potentials (MEPs) early in amyotrophic lateral sclerosis is lower than that in normal subjects. Kaji and Kimura[2] suggested that at least some fasciculations in amyotrophic lateral sclerosis are driven cortically without hyperexcitability of the motor neurons. We used a double magnetic cortical stimulation technique[4][5] to examine the motor cortical excitability of patients with early amyotrophic lateral sclerosis and compared the results with those for patients with spinal muscular atrophy and age matched normal controls.

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Subjects

Sixteen patients with amyotrophic lateral sclerosis (eight men and eight women, mean (SD) age 63·4 (6·5) years, duration of illness 13·5 (9·7) months), five with spinal muscular atrophy (five men; age 55·5 (5·9), duration of illness 12·0 (8·7) years), and 16 age matched normal controls were studied. Selection of patients with amyotrophic lateral sclerosis was based on the following criteria: (1) progressive muscular weakness and atrophy; (2) fasciculations of the affected muscles; (3) clinical signs of pyramidal tract lesion; (4) abnormal needle EMG results characteristic of anterior horn cell disease; (5) absence of sensory signs; sphincter abnormalities, and dementia; (6) absence of conduction block and abnormal temporal dispersion; (7) motor evoked potential (MEP) at rest > 1 mV without temporal dispersion and normal threshold stimulation intensity at rest that produces MEP; (8) MEP latency on electric cortical stimulation of low intensity shorter by more than 1·0 ms than that in magnetic stimulation for the selection of patients in which magnetic stimuli activate I waves. Selection of patients with spinal muscular atrophy was based on slowly progressive muscular weakness and atrophy without clinical signs of pyramidal tract lesion, as well as on criteria (4)-(8) for amyotrophic lateral sclerosis.

Methods

After informed consent, the patients and normal controls underwent transcranial magnetic stimulation (TMS). Each subject was seated in a comfortable reclining chair. Surface EMG recordings were made from the APB or flexor carpi radialis (FCR) muscle via surface electrodes attached in a belly tendon montage. Responses were amplified and filtered through Neuropack 4 (Nihon-Koden Ltd, Tokyo), the band pass ranging from 20 to 3 kHz. Transcranial stimulation was produced by a Magstim 200 magnetic stimulator (The Magstim Company, Whitland, Dyfed) or a Digitimer D180 high voltage electrical stimulator. For double cortical stimulation study magnetic stimulation was given by a figure of eight shaped coil, each loop having an outer diameter of 9 cm and a peak magnetic field of 2·2 T. The coil was held so that the electrical current in the junction region flowed from the anterior to the posterior direction over the lateral part of the motor strip. For routine MEP study, a round coil (14 cm outer diameter, 1·5

T) was used by conventional methods.[5] The threshold stimulation intensity at rest is defined as the stimulus required to produce a MEP of at least 0·1 mV amplitude in at least 50% of the trials. The central motor tract conduction time (CMCT) and MEP amplitude:M wave amplitude (MEP:M ratio) were estimated by the conventional method of Eisen and Shybel.[5]

The difference in the MEP latencies produced by electrical and magnetic stimuli was examined while the subjects maintained constant slight voluntary contraction (2%-5% of maximum) of the APB muscle. Electrical stimulation was given by a Digitimer D180 high voltage electrical stimulator through two Ag-AgCl EEG electrodes 9 mm in diameter, fixed at the vertex (cathode) and 7 cm lateral to the vertex (anode). The intensities of the electrical and magnetic stimulators were adjusted to evoke EMG responses of 1 mV.

DOUBLE MAGNETIC STIMULATION

For double stimulation two magnetic stimulators were connected to the same stimulating coil through a Bistim module (Magstim Company, Whitland, Dyfed, UK). During the examination the subject was asked to keep his or her eyes open so as not to fall asleep. Complete relaxation was ensured by monitoring the real time surface EMG activity at high gain. The subject received auditory feedback through a loudspeaker. The conditioning stimulus was applied to the same point on the scalp as the test stimulus at various conditioning-test (C-T) intervals. The respective intensities of the conditioning and test stimuli were adjusted to 90% and 130% of the relaxed threshold which was determined with the same figure of eight coil. In six of the normal subjects, the intensity of conditioning shock was varied from 60% to 100% of the threshold. We also compared the effect of a magnetic conditioning stimulus on the test responses evoked by magnetic or electrical test stimuli in four subjects. The intensity of the cortical electrical stimulus was adjusted to a level that produced a response of similar size to that evoked by the magnetic test stimulus at the relaxed APB muscle.

We used a condition-test design to investigate the time course of the effects. Conditioned and non-conditioned test shocks at different C-T intervals were intermixed randomly at intervals of four to six seconds. Eight to 12 responses per condition were collected, and their peak to peak amplitudes measured. At each C-T interval, the peak to peak size of

the conditioned responses was expressed as a ratio of the size of the unconditioned response (MEP size ratio).

We also examined the correlation between the MEP size ratios at C-T intervals of 2 and 3 ms and clinical findings, such as duration of illness, grip strength, and M wave size as an indicator for muscle atrophy.

EFFECT OF SUBTHRESHOLD MOTOR CORTICAL STIMULATION ON THE H REFLEX

We studied change in α-motor neuronal excitability after subthreshold magnetic cortical shock by the method of Cowan *et al*[6] in six of the normal controls and one patient with amyotrophic lateral sclerosis. The H reflexes were elicited in the FCR muscle by stimulating the median nerve in the cubital fossa electrically with 1 ms square wave constant current pulses of about motor threshold intensity. The intensity of the test was adjusted to obtain an H reflex 30%-50% of the maximal size. Twelve H reflexes conditioned by a TMS were intermixed randomly with six control H reflexes for each C-T interval. Magnetic stimulus as the conditioning shock was timed to precede the test shock by corresponding intervals of 0-10 ms in the magnetic double stimulation of the motor cortex. The time between each subsequent H reflex was five seconds.

Multiple analysis of variance (MANOVA) was used for the statistical analysis of the differences in MEP size ratios at each C-T interval in normal subjects and patients; and the unpaired t test was used for the analysis of MEP threshold, CMCT, MEP size, M size, and MEP:M ratio between normal subjects and patients.

Results

The table shows the results of the routine MEP studies. Because of the criteria used for case selection, patients with amyotrophic lateral sclerosis with an early stage of motor tract involvement were selected; CMCT, MEP threshold, and MEP:M ratio did not differ from those of controls although the M wave and MEP sizes were small. Also, in spinal muscular atrophy the MEP and M sizes were small, but CMCT, MEP threshold, and MEP:M ratio were normal.

DOUBLE MAGNETIC STIMULATION

In normal subjects the size of response to test shock was significantly reduced by conditioning shock at a short C-T interval when the intensity of conditioning shock was 90% of the threshold in both the APB (fig 1A and C) and FCR muscles. This suppression was significant (P < 0·01) at C-T intervals of 1–4 ms in the APB muscle and at intervals of 1–3 ms in the FCR muscle, and was nearly significant at 5 ms in the APB muscle and at 4 and 5 ms in the FCR muscle (P < 0·05). The suppression was followed by facilitation at a C-T interval of 10 ms in both muscles (P < 0·01). When the intensity of the conditioning shock ranged from 60, 70, 80, 90, or 100% of the threshold for excitation, the sizes of responses to condi-

Results of routine MEP study

	ALS (n = 17)	SMA (n = 5)	Normal subjects (n = 17)
MEP threshold (%)	55·7 (11·4)	58·8 (4·5)	53·7 (7·9)
CMCT (ms)	6·0 (1·3)	7·0 (1·1)	6·3 (0·8)
MEP size (mV)	4·2 (2·1)	4·7 (1·70)	6·2 (2·3)
M size (mV)	7·2 (4·4)	7·1 (3·9)	14·1 (4·6)
MEP:M ratio	65·8 (29·2)	51·8 (8·3)	45·8 (15·5)

Values are means (SD). ALS = Amyotrophic lateral sclerosis; SMA = spinal muscular atrophy.

Figure 1   Effect of subthreshold conditioning stimulation on MEP size in normal subjects and in patients with amyotrophic lateral sclerosis (ALS). (A) MEP wave forms of the non-conditioned test and conditioned responses in normal controls and (B) in patients with amyotrophic lateral sclerosis. (C) Time courses of the effects as ratios of the mean conditioned to non-conditioned MEP size in the normal controls, patients with amyotrophic lateral sclerosis, and patients with spinal muscular atrophy (SMA). Values below 1 represent suppression. Vertical bars are SD. Statistical analysis was performed on MEP ratios between patients with amyotrophic lateral sclerosis and normal subjects, and between patients with spinal muscular atrophy and normal subjects.
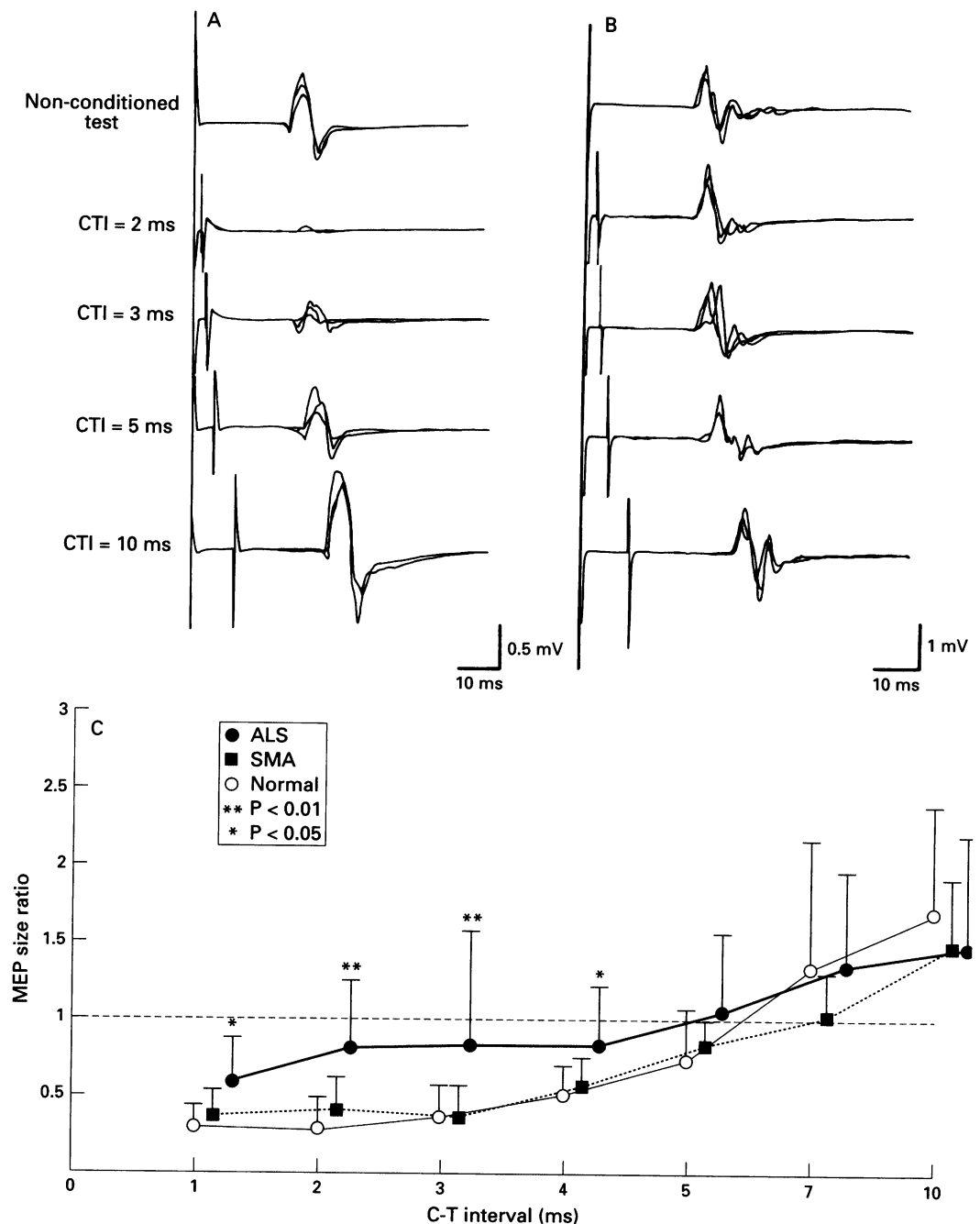
tioned test shocks were suppressed (38·8, 22·2, 19·9, 18·8, and 28·4% of the response size to non-conditioned test shock respectively). When the test shock was evoked by electrical stimuli, the response to test shocks was not suppressed by the conditioning magnetic stimulus (MEP size ratio 1·06 (SD 0·65) at a C-T interval of 3 ms).

For patients with amyotrophic lateral sclerosis, by contrast, the reduction of size of response to test shock by conditioning shock was significant only at the C-T interval of 1 ms, and was much less prominent at 2 and 3 ms than that in normal subjects (P < 0·01; fig 1B and 1C). The facilitation at 10 ms was not clear, but the difference from that in the normal subjects was not significant.

For the patients with spinal muscular atrophy the reduction of size of response to test shock by conditioning shock at short C-T

intervals was similar to that in the normal controls, and statistically there was no difference between the two groups (fig 1C).

There was no clear correlation between the MEP size ratios at C-T intervals of 2 and 3 ms and clinical findings, duration of illness, grip strength, and M wave size.

EFFECT OF SUBTHRESHOLD MOTOR CORTICAL STIMULATION ON THE H REFLEX

The effect of subthreshold magnetic cortical stimulation on the H reflex in the normal controls was facilitation (P < 0·01) at C-T intervals of 0–1·5 ms followed by a rapid decrease in excitation to the baseline. Subsequently, there was a second smaller and longlasting facilitation of the H reflex. In a patient with amyotrophic lateral sclerosis in whom there was no suppression of the responses on double magnetic cortical stimulation at short C-T

Figure 2 Effect of subthreshold scalp stimulation on H reflex size. Time courses of the effects as ratios of the mean conditioned to non-conditioned H reflex size in normal controls and one patient with amyotrophic lateral sclerosis.
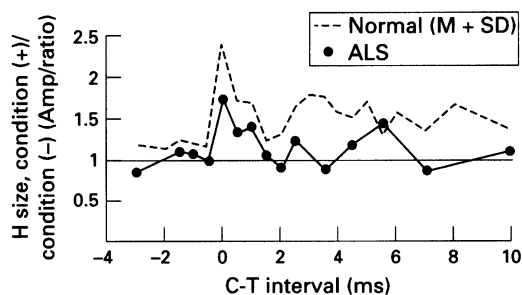
intervals, the effect of the conditioning shock on the H reflex was in the normal range (fig 2).

Discussion

Magnetic subthreshold conditioning stimulus over the hand area of the cortex suppresses the responses produced in the relaxed hand muscles by a suprathreshold magnetic test stimulus at short C-T intervals in normal young adults.[4 7 8] Kujirai et al[4] suggested that the suppression at C-T intervals of 1–6 ms is produced by an action on cortical, rather than by spinal, excitability, because subthreshold magnetic conditioning stimuli do not produce a 5 ms period of inhibition in the forearm H reflex[9] even though the same stimuli suppress responses evoked in the same muscles by suprathreshold magnetic test stimuli. Moreover, a magnetic conditioning stimulus given over the hand area did not produce suppression of responses evoked in active hand muscles by small anodal electrical stimulation.[4] Our experiments on normal, aged subjects gave results similar to those of Kujirai et al.[4] These results indicate that the refractory period of corticospinal axons, after-hyperpolarization in the cell body, or corticospinal recurrent collaterals are not important contributors to this suppression.

In the patients with amyotrophic lateral sclerosis the suppression at short C-T intervals was much less prominent than that in the age matched controls. If the MEP threshold increases in the late stage of amyotrophic lateral sclerosis and the intensity of the conditioning shock increases, newly excited cortical interneurons or fibres may affect suppression even when the mechanism of this suppression is unchanged; but we selected patients with normal MEP thresholds. The reduction of the motor neuron pool seen in our patients with amyotrophic lateral sclerosis probably has little effect on this suppression because it was normal in patients with spinal muscular atrophy who also showed an M wave size that was reduced as much as in amyotrophic lateral sclerosis.

Although the exact site of the activation of the cortical neuron by magnetic stimulation has yet to be determined, the threshold for the I wave is lower than that for the D wave when stimulated with low intensity.[10 11] Recent research, however, suggests that even low intensity magnetic stimuli may activate the D wave.[12] If test stimuli excite the D wave in patients with amyotrophic lateral sclerosis, the suppression should be reduced because of the

summation of the D wave and subliminal increase in the excitability of the α-motor neuron by the conditioning[4 9 13]; but we selected patients with amyotrophic lateral sclerosis in whom the MEP latency produced by electrical cortical stimulation was shorter by more than 1·0 ms than that produced by magnetic stimulation when electrical and magnetic stimuli of low intensity were applied during voluntary muscle contraction. This indicates that magnetic test stimuli predominantly activated I waves in our patients with amyotrophic lateral sclerosis.[10]

We do not know the actual site responsible for the lack of the MEP suppression, but speculate that it is at the level of the cerebral cortex, rather than the spinal cord because the effect of the conditioning cortical shock on the H reflex size was in the normal range. Although the impairment of intracortical inhibition in amyotrophic lateral sclerosis seems to be the simplest explanation for the present results, changes in other actions which may contribute to the suppression, such as presynaptic effects on the H reflex pathway, postsynaptic effects on possible interneurons in the corticospinal pathway, and change of recruitment order of pyramidal tract neurons cannot be excluded.[4]

For some patients with amyotrophic lateral sclerosis, it was not easy to keep their target muscles at rest. Although the electrical silence of the target muscle was confirmed by audio and visual monitorings when double cortical stimuli were applied, we could not monitor the descending discharges of the corticospinal tract which are subliminal for activating α-motor neurons. An increase in such descending discharges might contribute to the lack of the MEP suppression because this suppression decreased during voluntary contraction even in normal subjects.[7] If so, it can be explained as a representation of the hyperexcitability of the pyramidal tract neuron.

There are many hypotheses about the cause of amyotrophic lateral sclerosis. One holds that glutamate, the primary excitatory neurotransmitter in the CNS, accumulates to toxic concentrations at the synapses, causing neurons to die, probably through a calcium dependent pathway. This hypothesis is supported by results of a controlled trial in which the antiglutamate agent reluzole did not stop but slowed down progression of the illness.[14] In line with this, Rothstein et al[15] reported decreased high affinity glutamate uptake by synaptosomes from the motor cortex and spinal cord. If true, the increased concentration of extracellular glutamate may cause prolonged overexcitation of pyramidal tract neurons, spinal motor neurons, or both, and this may explain the lack of suppression on double cortical stimulation of our patients with amyotrophic lateral sclerosis.[15] We plan to investigate the effect of this antiglutamate agent on the suppression.

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HISTORICAL NOTES

Duane's syndrome

Students of neurology commonly encounter, but don't always recognise, a type of congenital squint that arises owing to fibrosis in the lateral rectus muscle, which retracts the globe and narrows the palpebral fissure of the eye when it is adducted. The cause of the primary lesion is often unknown. A not uncommon phenomenon, it was reported by Duane.

In 1905 he described the essential features succinctly in the title of his paper[1]:

"Congenital deficiency of abduction, associated with impairment of adduction, retraction movements, contraction of the palpebral fissure and oblique movements of the eye."

This was later called Duane's retraction syndrome. An autosomal dominant form with four generations described in one kindred was later reported.[2] There are also associations with deafness and the Klippel Feil anomaly, known as the Wildervanck syndrome, and a report of associated congenital defects of the radius.

Alexander Duane (1858–1926) was born in Malone, New York into a distinguished and talented family. A rather authoritarian background probably influenced his work. His father was an army General with a good knowledge of mathematics, which he passed on to his son. His mother, having considerable literary accomplishments, instructed him in English usage that he later employed in contributions to several dictionaries. Duane attended school in Cincinnati and read Medicine at the College of Physicians and Surgeons [Columbia University]. Trained in ophthalmology he practised in New York. In 1903 he translated the Austrian Fuchs's *Textbook of Ophthalmology*, which ran to eight editions. His work on optics, disordered eye movements, accommodation, and refraction led to election as president of the American Ophthalmological Society in 1924. There were many sides to Duane's character: literary, medical, and naval. He wrote an instructional text on *Rules for signalling on land and sea* (1899) based on his experience as lieutenant in the Spanish-American war. Later, he served in the first world war as a rather elderly signal officer.

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