

# Cortical Excitability in Amyotrophic Lateral Sclerosis: A Clue to Pathogenesis

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**ABSTRACT:** Motor evoked potentials (MEPs) were recorded from selected non-wasted, non-denervated hand muscles in 40 patients with Amyotrophic Lateral Sclerosis (ALS) with both upper and lower motor neuron signs. In most the compound muscle action potential (CMAP) of the target muscle was normal. Compared to the control group, cortical threshold in ALS varied considerably and there was a significant ( $r^2 = 0.702$ ) inverse, exponential, correlation between cortical threshold and MEP/CMAP ratio. There was a linear correlation between threshold and disease duration ( $r^2 = 0.66$ ) so that early in the disease threshold was normal and later the motor cortex could not be stimulated. It is suggested that early in ALS normal threshold reflects glutamate-induced hyper-excitability of the corticomotoneuron. The findings lend support to the hypothesis that ALS is primarily a disease of the corticomotoneuron.

**RÉSUMÉ:** Excitabilité corticale dans la sclérose latérale amyotrophique: un indice de sa pathogénèse. Nous avons enregistré les potentiels évoqués moteurs (PEM) de muscles de la main non-atrophiés et non-dénervés chez 40 patients atteints de sclérose latérale amyotrophique (SLA) ayant des signes d'atteinte du neurone moteur central et périphérique. Chez la plupart, le potentiel d'action musculaire composé (PAMC) du muscle cible était normal. Comparé au groupe contrôle, le seuil cortical variait considérablement dans la SLA et il existait une corrélation inverse significative ( $r^2 = 0.702$ ), exponentielle, entre le seuil cortical et le rapport PEM/PAMC. Il existait une corrélation linéaire entre le seuil et la durée de la maladie ( $r^2 = 0.66$ ), de telle sorte que le seuil était normal au début de la maladie et par la suite, le cortex moteur ne pouvait plus être stimulé. Nous suggérons que, tôt dans la SLA, le seuil normal reflète l'hyperexcitabilité du neurone moteur cortical induite par le glutamate. Ces observations supportent l'hypothèse que la SLA est avant tout une maladie du neurone moteur cortical.

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Transcranial magnetic stimulation excites the cortico-spinal tracts transsynaptically,<sup>1</sup> activating the fast conducting corticomotoneurons,<sup>2,3</sup> which connect monosynaptically with the anterior horn cells. The corticomotoneuronal system is well developed in primates and particularly so in humans.<sup>4,5</sup> This system is largely responsible for the highly fractionated movements that primates enjoy. Connections are most abundant to the hand motor neuron pool;<sup>6,7</sup> but in humans they have been demonstrated to all motor neuron pools except those innervating the external ocular muscles and bladder, which are typically spared in Amyotrophic Lateral Sclerosis (ALS).<sup>8</sup>

This anatomical arrangement in humans and the lack of a natural or, thus far, induced animal model that truly mimics ALS<sup>9</sup> and the primitive nature of the corticomotoneuronal system in non-primates, has led to the hypothesis that disease of the corticomotoneuron is the initial event in ALS and that demise of the anterior horn cell is secondary to anterograde effects.<sup>10,11</sup> Charcot<sup>12</sup> had a similar concept of ALS over a century ago.

Anatomical proof for this hypothesis requires demonstration of degeneration in parts of the primary motor area connected with spinal segments in which the motor neurons were unaffected

at the time of death and coincident degeneration of those corticomotoneurons connected to already degenerated anterior horn cells.<sup>13</sup> Pathological proof is probably not possible, since there is not a one to one relationship between the corticomotoneuron and the anterior horn cell. Each anterior horn cell receives input from several, maybe many, corticomotoneurons and one corticomotoneuron makes monosynaptic connections with anterior horn cells of its own muscle as well as agonists and even antagonists.<sup>14-16</sup> The anatomic relation is further fraught with difficulty because anterior horn cells "overloaded" as a result of sprouting initiate their own effects at a spinal level. As a result, quantitative comparison of loss of corticomotoneurons versus anterior horn cells would be difficult, if not impossible, to evaluate after death.

A different approach is through the use of transcranial magnetic stimulation. This, together with conventional studies used to evaluate the peripheral nervous system, may enable one to demonstrate evidence for early corticomotoneuronal versus anterior horn cell disease.

Central motor conduction and motor evoked potential (MEP) latency are frequently normal in ALS even in the presence of

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motor deficit affecting fine finger movement.<sup>17</sup> Here we report changes in the threshold to cortical stimulation and the ratio of the MEP to the compound muscle action potential (CMAP), both of which are measures of the integrity of the corticomotoneuron.

## METHODS

### Subjects

Forty patients with ALS gave informed consent for investigation. The majority were studied within 15 months (range 3 - 30 months) of onset of their disease, timed from initial symptoms. Their mean age was  $57.9 \pm 12.4$  years; there were 21 men. The protocol employed was approved by the Human Ethics Committee of the University of British Columbia.

A diagnosis of ALS was based upon the neurological history and examination and laboratory tests.<sup>18</sup> Patients were included if: 1. There was a history of progressive asymmetrical muscle weakness over weeks or months. 2. There was clinical evidence of both upper and lower motor neuron dysfunction in the face of normal eye movements, sphincter function and sensory examination. 3. Absence of significant motor or sensory conduction abnormalities or motoneuronopathy with multifocal motor conduction block.<sup>19,20</sup> 4. Electrophysiological evidence of anterior horn cell disease<sup>21</sup> and 5. Normal imaging (CT and/or MRI) of the brain and spinal cord.

Patients with purely progressive muscular atrophy, previous poliomyelitis or postpoliomyelitis syndrome, primary lateral sclerosis, monomelic amyotrophy and a family history of ALS were excluded and patients who had multifocal motor conduction block. Also excluded were patients with severe systemic disease occurring within 2 years of developing symptoms of ALS.

Thirty-five subjects, without neurological or other disease, matched for age, were also studied.

### Magnetic Stimulation

Motor evoked potentials (MEPs) were elicited by transcranial magnetic stimulation using a Dantec circular coil, with an outer diameter of 10.5 cm and a 6.5 cm central hole. The subject was seated comfortably in a temperature-maintained environment (20 - 22°C). Electromyographic responses were recorded from the either thenar or hypothenar muscles employing surface electrodes filled with electrogel. The  $G_1$  electrode was placed over the muscle belly endplate and the  $G_2$  electrode over the distal tendinous insertion. MEPs were recorded from whichever of the 4 selected muscles had the largest compound muscle action potential (CMAP). No attempt was made to record MEPs from muscles that were severely wasted or which demonstrated marked evidence of denervation (fibrillation of positive sharp waves).

MEPs were elicited with the muscle at rest. The coil was placed flat over the vertex but moved as necessary to obtain optimal responses.<sup>22</sup> Audio feedback was used to ensure lack of voluntary muscle activity during cortical stimulation. Relaxation was defined as the absence of EMG activity at a display gain of 20  $\mu$ V/division. In the event that the target muscle was fasciculating, care was taken to deliver the cortical stimulus in a fasciculation-free period. Ten to twenty responses were obtained and the ones with the shortest onset latency and largest peak to peak

amplitude were measured. The output of the stimulator was 25% - 30% above threshold.

Threshold is a measure of excitation of the corticomotoneuron and is defined as the strength or output of the stimulator, expressed as the percentage, required to elicit a potential of  $> 20\mu$ V amplitude in 3 out of 5 consecutive trials of stimulation with the coil in the optimal position.<sup>23-25</sup> Threshold measurements were excluded from the ALS data if a spontaneous fasciculation coincided with the magnetic stimulus.

The MEP/CMAP ratio was measured by dividing the maximum amplitude compound muscle action potential (CMAP) elicited by supramaximal electrical stimulation of the median or ulnar nerves at the wrist into the largest cortically evoked response. Central motor delay (CCT) was derived from the latency difference of the MEPs elicited by placing the coil over the cortex and the lower cervical spine in the midline (Eisen and Shtybel 1990).

Potentials were considered abnormal if any of the following pertained: absent response, latency  $\geq 25.0$  msec, CCT  $\geq 11.5$  msec, MEP amplitude  $\leq 1.2$  mV, MEP/CMAP ratio  $\leq 10\%$ , threshold  $\geq 67.5\%$ . A CMAP of  $\leq 6.9$  mV was also considered abnormal.

## RESULTS

Duration of disease, determined from the onset of initial symptoms, ranged from 3 - 30 months (mean =  $8.35 \pm 7.6$  months). In 14 (35%) of cases the initial symptoms were bulbar in nature. There was no significant correlation between any of the MEP abnormalities and, either general clinical deficit (i.e., bulbar versus non-bulbar predominance, marked spasticity or very brisk reflexes) or focal hand neurological deficit (i.e., difficulty with fine finger movements or brisk finger flexion).

Individual patient values for latency, motor evoked potential (MEP) amplitude, compound muscle action potential amplitude (CMAP), MEP/CMAP ratio and cortical threshold are plotted in Figure 1. The upper or lower normal limits, indicated by the arrows, were derived from the aged-matched control group. The frequency of abnormalities for each measurement is given in Table 1. Mean group latency and central motor conduction time were modestly but significantly prolonged compared to the aged-matched control group (see Table 1). There was no difference in the patient and control CMAPs and only 7 patients had a CMAP that was below normal. However, the cortically evoked motor potential (MEP) amplitude and MEP/CMAP ratio were significantly reduced in the patients.

Values for cortical threshold in the normal subjects fell within a fairly narrow range and there was no relation between it and MEP/CMAP ratio (see Figure 2A). This contrasted with the wide range of threshold in patients with ALS. Three had thresholds lower than the lowest recorded in the control group and in 9 patients (22.5%) it was not possible to elicit a potential even at maximum output of the stimulator. In the ALS patients there was a highly significant ( $r^2 = 0.702$ ), exponential ( $y = ax^b$ ), relationship between cortical threshold and MEP/CMAP ratio (Figure 2B) but not between cortical threshold and MEP amplitude (Figure 3).

There was also a significant positive linear correlation ( $r^2 = 0.658$ ) between cortical threshold and disease duration (Figure 4).

## DISCUSSION

Earlier studies in ALS used electrical stimulation of the motor cortex and showed that there was a modest prolongation of central motor conduction time and frequently marked attenuation or in some cases absence of the MEP.<sup>26,27</sup> Schriefer et al.<sup>28</sup> studied 22 ALS patients using transcranial magnetic stimulation and found only a weak correlation between central motor conduction prolongation and other MEP abnormalities and hyper-reflexia of the limb studied including brisk finger flexion. There

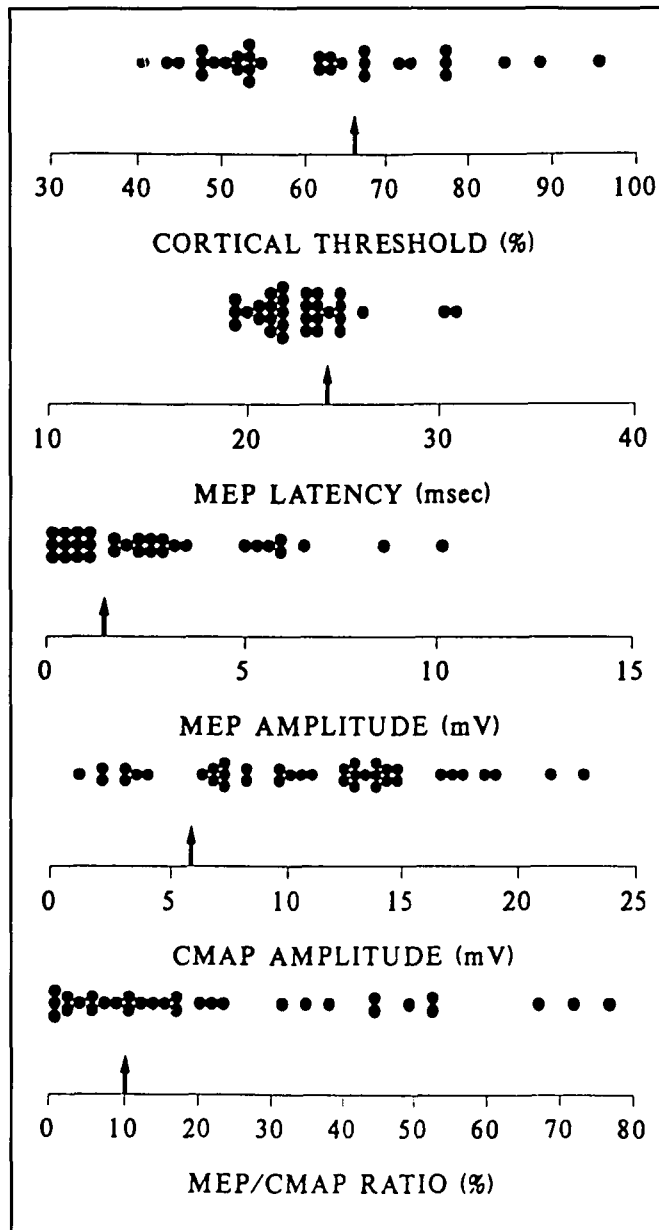


Figure 1 — Scatterplots for different motor evoked potential (MEP) characteristics in 40 patients with ALS. No response was obtained in 9 patients. The hypothenar compound muscle action potential amplitude (CMAP) is also shown. The arrows indicate the upper (for threshold, latency) and lower (for MEP and CMAP amplitudes and MEP/CMAP ratio) normal limits. The normal limits which were derived from the control group are 2.5 SD above or below the normal mean.

was no correlation between central motor conduction and impairment of fine finger movement or hypothenar muscle weakness. Abnormal MEPs were also recorded in some patients with a normal clinical examination of the limb studied and normal MEPs were recorded in 5 cases who had definite neurological deficit. Subsequently, Eisen et al.,<sup>29</sup> recording from several upper limb muscles, found that an absent MEP was most frequent in patients with severe bulbar features.

Recent reports indicate that prolongation of central conduction in ALS is more likely to be detected by electrical rather than magnetic stimulation,<sup>30</sup> but that a reduced MEP/CMAP ratio is the commonest abnormality with magnetic stimulation. In the present study MEP amplitude, MEP/CMAP ratio and cortical threshold were abnormal in about 50% of the patients. The frequency of these abnormalities in combination approached 75%. Latency or central motor delay were abnormal with a much lower frequency and were never abnormal if the other MEP characteristics were normal.

The majority of our patients were seen early in the course of their disease and most were ambulatory. We found no correlation between severity or type of motor deficit and electrophysiological abnormalities.

Factors determining the MEP/CMAP ratio and cortical threshold in ALS, a disease affecting both the corticomotoneuron and the anterior horn cell, are complex and interactive. Assuming an optimal coil position, they include: 1. Survival or demise of the corticomotoneuron relative to the anterior horn cell (i.e., the number of functioning corticomotoneuronal connections). 2. The number, size and synchrony of descending volleys initiated by the stimulus and their ability to raise the anterior horn cell to threshold.<sup>31</sup> 3. The cell membrane properties of both the corticomotoneuron and the anterior horn cell. 4. Modifying central and peripheral, excitatory or inhibitory influences, such as spasticity.

Table 1: Motor Evoked Potential Measurements in ALS

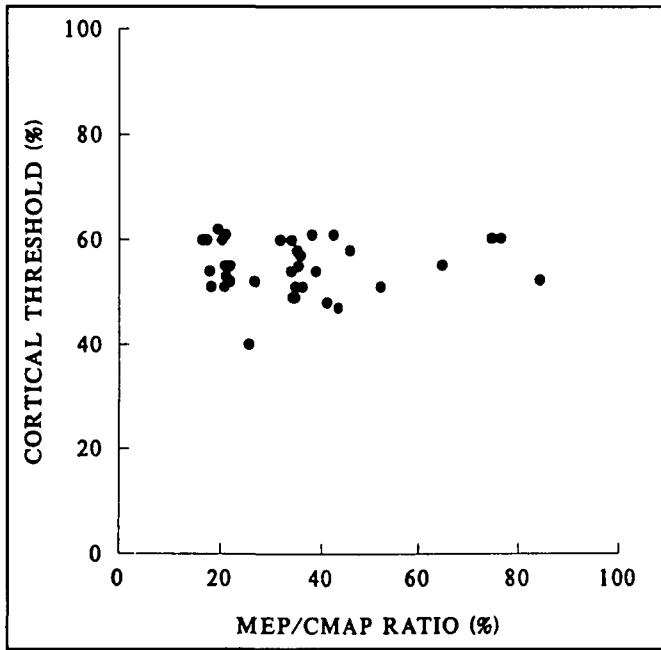
	Normal (n = 35)	ALS (n = 40)	p Value
AGE	56.2 ± 13.4	57.9 ± 12.4	NS
THRESHOLD (%)	54.8 ± 5.1	63.6 ± 8.2	NS
LATENCY (msec)	21.2 ± 1.5	23.0 ± 2.8	< 0.02
MEP AMPLITUDE (mV)	4.9 ± 4.6	2.8 ± 2.6	< 0.01
CMAP (mV)	13.8 ± 4.3	11.7 ± 5.7	NS
MEP/CMAP RATIO (%)	35.5 ± 17.4	21.9 ± 21.3	< 0.02
CMCT	7.8 ± 1.5	10.5 ± 1.9	< 0.01

(Values are the mean ± one standard deviation).

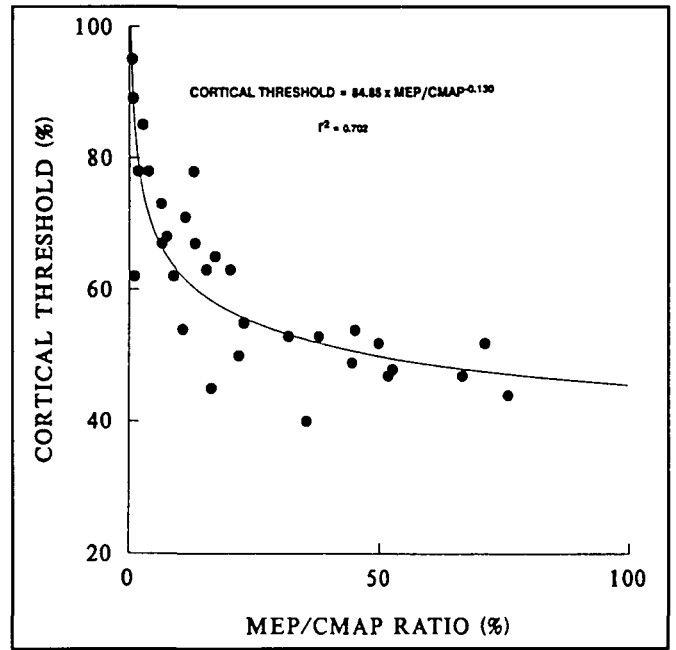
MEPs were recorded from the resting thenar or hypothenar muscles. CMAP = compound muscle action potential. CMCT = central motor conduction time. Threshold is defined as the output (%) needed to elicit a potential of ≥ 20 μV in 3/5 consecutive trials. The number of patients with an abnormality of each measurement is given below the mean. For MEP measurements this number includes 9 patients with absent responses.

The above factors are largely difficult, or impossible, to control. Nevertheless, MEPs were selectively recorded from non-wasted, non-denervated hand muscles, indicated by the absence of fibrillation or positive sharp waves, associated with a normal CMAP amplitude in more than 80% of the patients. Under these

circumstances it is reasonable to conclude that reduction in the MEP/CMAP ratio was due primarily to corticomotoneuronal rather than anterior horn cell disease or demise. This view is supported by the significant relationship between MEP/CMAP ratio and cortical threshold (Figure 2A) and the absence of any



A



B

Figure 2 — A. In normal subjects values for cortical threshold are clustered and show no particular relation to cortical threshold. B. Relationship between threshold to cortical stimulation in ALS and MEP/CMAP ratio. The power curve shown and given by  $Y = A X^b$  best fitted the data.

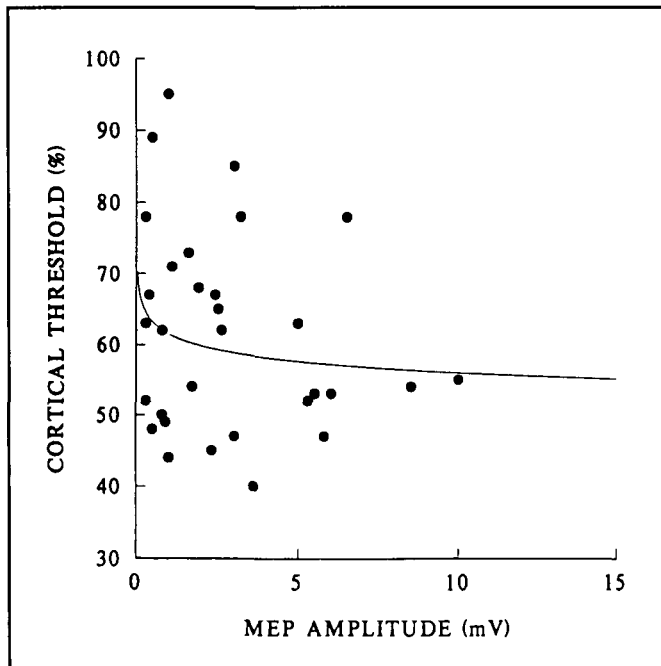


Figure 3 — ALS patients. Lack of any meaningful correlation between MEP amplitude and cortical threshold.

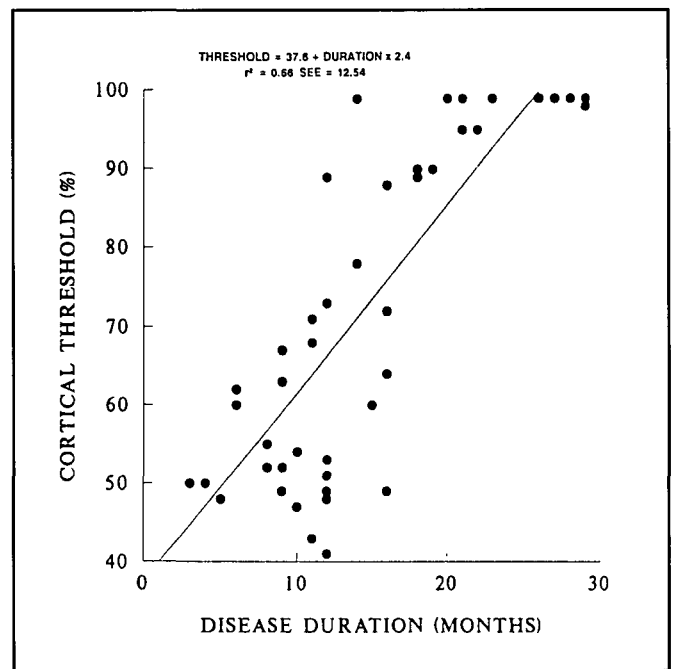


Figure 4 — Relation between cortical threshold and disease duration in ALS is linear ( $r^2 = 0.66$ ). Nine points are shown at values for cortical threshold = 99; these are patients in whom no response was obtained. Their values were not used in calculating the regression coefficients.



correlation between threshold and MEP amplitude (Figure 3).

The mean cortical threshold for normal hand muscles (54.8%) and its narrow range is similar to other recent reports.<sup>23,25</sup> Threshold is age-dependent, and is high in infants, falling to adult values by the second decade of life.<sup>32</sup> The protracted time for cortical threshold to fall to adult values compared to the attainment of adult central motor conduction velocities reflects slow maturation of corticomotoneuronal connections.<sup>32</sup> One might have anticipated that in ALS, a disease that affects the corticomotoneuronal system, cortical threshold would be uniformly raised. This was not the case; many patients had values in the normal range for aged matched controls and a few had low values. Although values for different individuals varied considerably there was a striking and significant exponential relationship between threshold and MEP/CMAP ratio and linear relationship between threshold and disease duration.

Given the normal amplitude CMAP in the majority of patients and the lack of active denervation (fibrillation or positive sharp waves) in the target muscle, it can be reasonably assumed that motor neuron pool was sufficiently adequate to preclude it as a likely cause of increased cortical threshold in the majority of our patients. In support of this we have noted that in postpoliomyelitis syndrome cortical threshold is normal even when the MEP is of small amplitude and recorded from quite severely wasted muscles (unpublished data). Therefore, corticomotoneuronal death or dysfunction is the most likely cause for the increasing cortical threshold that occurs as ALS progresses. It is possible that dendritic thinning, which has been identified as an early feature of the disease<sup>33</sup> is responsible for the time-related rise in cortical threshold.

Paradoxically normal, or low thresholds, which have been previously observed in ALS,<sup>24</sup> may also result from the effect of voluntary muscle contraction.<sup>34-36</sup> This was carefully avoided during stimulation. Caramia et al.<sup>24</sup> noted that fasciculation was present in the muscles from which low or normal threshold MEPs were recorded. They argued that the hyperexcitability of the anterior horn cells, which might account for some fasciculation in ALS, would equally make them more receptive to the descending cortical volleys. We could not confirm that patients with prominent fasciculations were necessarily those with normal or low cortical thresholds. About half the number of target muscles were not fasciculating and even in those patients with fasciculations, threshold measurements were only accepted when the MEP was elicited during a fasciculation-free period. In some of the patients with marked fasciculation it was not possible to elicit a MEP.

Another plausible explanation for the ready excitability of the motor cortex in ALS lies in glutamate excitotoxicity. There has been much recent interest in the amino-acid, excitotoxic pathogenesis of ALS; specifically as it relates to glutamate transmission.<sup>37</sup> Glutamate is the putative transmitter of the corticomotoneuronal system that stimulates lower motor neurons<sup>38</sup> and disturbed function of the NMDA receptor in the motor cortex and spinal cord may be implicated in neuronal death in ALS. NMDA receptors are distributed throughout the spinal grey matter of the human spinal cord with foci of high density binding sites corresponding in distribution to the anterior horn cells<sup>39</sup> and glutamate dehydrogenase is elevated and transmitter aminoacids (glutamate and aspartate) are reduced in the same regions of the spinal cord in patients dying with ALS.<sup>40</sup> Recent

studies have shown a defect in high-affinity glutamate transport, with a 70% reduction in ALS motor cortex. Faulty transport probably induces toxic and pathogenic levels of extracellular glutamate.<sup>41</sup>

If disordered glutamate metabolism, or some other excitotoxic aminoacid, is responsible for lowering the threshold to cortical magnetic stimulation it might be anticipated that with disease progression, as corticomotoneurons are "excited to death", threshold will rise and eventually the corticomotoneurons will become inexcitable. The results depicted in Figure 4, which show a linear correlation between cortical threshold and disease duration, support this concept.

In conclusion we have shown that early in the course of ALS, cortical threshold, which correlated with the MEP/CMAP ratio, was paradoxically normal and as the disease progressed there was an exponential rise in threshold associated with a fall in the MEP/CMAP ratio. This series of events, which might reflect glutamate-induced corticomotoneuronal excitotoxicity, partially support the concept that ALS may primarily be a disease of the corticomotoneuron.

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