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A new neurophysiological approach to assess central motor conduction damage to proximal and distal muscles of lower limbs

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HIGHLIGHTS

- TMS using the double cone coil and high voltage electrical stimulation of lumbosacral roots allows bilateral and simultaneous assessment of central motor pathways to proximal and distal muscles of lower limbs.
- A strict control of voluntary facilitation using a predefined sequence of movements of constant amplitude and the use of MEP averaging significantly reduce MEP area variability.
- The described method provides an extensive mapping of both conduction slowing and conduction failure in central motor pathways to lower limbs in clinical application.

ABSTRACT

Objective: To develop a neurophysiological method to explore central motor pathways to proximal and distal muscles of lower limbs.
Methods: MEPs to transcranial magnetic stimulation using the double cone coil were bilaterally and simultaneously recorded from vastus medialis, tibialis anterior and flexor hallucis brevis. Voluntary facilitation was controlled using a predefined sequence of movements of constant amplitude. Compound motor action potentials elicited by maximal high voltage electrical stimulation of lumbosacral roots (root-CMAPs) were recorded from the same muscles to obtain the corresponding peripheral conduction times. We studied 28 healthy subjects and 28 multiple sclerosis (MS) patients with no or mild motor impairment.
Results: The described facilitation procedure and the averaging of 5 MEPs reduced area variability to about 10%. In MS patients conduction slowing and/or MEP area reduction in at least one muscle was found in 91.7% of cases, with significant correlation with individual motor impairment.
Conclusions: Combined use of stable MEPs and maximal root-CMAPs was able to detect both conduction slowing and conduction failure in central motor pathways to proximal and distal districts of lower limbs in MS patients.
Significance: The proposed method provides an extensive electrophysiological mapping of central motor impairment of lower limbs in clinical application.

1. Introduction

Motor Evoked Potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) are routinely used in clinical settings to evaluate central motor conduction slowing, particularly in multiple sclerosis (MS) patients (Rothwell et al., 1991; Groppa et al., 2012). In lower limbs, however, MEPs recording is usually limited to single muscles, generally the tibialis anterior (TA) or the flexor hallucis brevis (FHB) (Colombo et al., 2000; Humm et al., 2003; Rico et al., 2009).

We have recently demonstrated that bilateral, maximal compound motor action potentials (CMAPs) from several muscle districts, directly providing total Peripheral Conduction Time (PCT), can be elicited bilaterally by using High Voltage Electrical Stimulation (HVES) of lumbo-sacral nerve roots at their origin from the spinal cord (Troni et al., 2011). Most importantly, the method provides PCTs also from proximal districts, such as vastus medialis

Abbreviations: BMRC, British Medical Research Council scale; BS11, Eleven Point Box scale; CMCT, central motor conduction time; CMAP, compound muscle action potential; MS, multiple sclerosis; FHB, flexor hallucis brevis muscle; HVES, high voltage electrical stimulation; MEP, motor evoked potential; PCT, peripheral conduction time; TA, tibialis anterior muscle; TMS, transcranial magnetic stimulation; VM, vastus medialis muscle.

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(VM), which are not obtainable with the F-wave method (Rivner, 1998).

In the present study we applied TMS by using the double cone coil to obtain MEPs in the same districts where maximal CMAPs elicited by HVES were recorded. Central Motor Conduction Time (CMCT) was calculated by subtracting PCT from the latency of the corresponding MEP. Although conduction failure (conduction block and axonal damage) is clearly related to MEP area reduction, area variability in serial recordings actually prevents a reliable use of MEP area in clinical practice (Hess et al., 1987; Kiers et al., 1993). This limit prompted Magistris et al. to develop the triple stimulation technique that cancels intra-trial MEP variability (Magistris et al., 1998, 1999). A further aim of our paper is to demonstrate that, by using a different methodological approach, variability of the raw MEPs can be significantly decreased if responses are recorded during a carefully designed and controlled voluntary muscle activation and the average of few MEPs is used.

We tested the applicability of the method in MS patients.

2. Methods

2.1. Subjects

We studied 28 healthy subjects as controls (12 males and 16 females, mean age 37.8) and 28 MS patients (13 males and 15 females, mean age 41.2). In all subjects a previous history of seizures was excluded. Four MS patients with no or mild motor impairment (1 with clinically isolated syndrome, 1 with primary progressive MS and 2 with relapsing-remitting MS), and 7 controls underwent a preliminary study aimed to design a methodological strategy to reduce intra-trial MEP area and latency variability. The remaining 24 MS patients (Table 1) and 21 controls, matched for age and sex, underwent the full mapping procedure of central motor function. In subjects with MS, the degree of motor damage, expressed by Kurzte's Scale Pyramidal Functional Score (PyFS), ranged from 0 to 3, with most patients presenting mild or no motor disability (PyFs ranged from 0 to 2 in 21 out of 24 patients). In each muscle district motor impairment was evaluated using the British Medical Research Council (BMRC) scale for muscle strength, according to Neurostatus Scoring for assessment of Kurtzke's Functional Systems and Expanded Disability Scale in multiple sclerosis.

The study was approved by the Ethics Committee and written informed consent was obtained from all the subjects studied.

2.2. Identification of recording sites

In all subjects we first located the optimum recording sites giving maximal CMAPs with a regular shape and a sharp initial negative deflection. CMAPs were recorded with a pair of surface electrodes (Ambu® Neuroline 715, diameter 0.8 cm) placed 4 cm apart in a belly-tendon arrangement, in symmetrical sites of VM, TA and FHB muscles of both sides.

Table 1
Clinical features of a MS population studied by clinical application of the described method (n = 24) EDSS = Expanded Disability System Scale. FS = Functional System. CIS = Clinically Isolated Syndrome. RR = Relapsing Remitting. SP = Secondary Progressive. PP = Primary Progressive.

Characteristic		
Age	Mean (range)	41.5 (25–60)
Sex (female)	N (%)	13 (54.2%)
EDSS	Mean (range)	2.2 (0–6.0)
Pyramidal FS 0 / 1	N	6/5
Pyramidal FS 2 / 3	N	10/3
Clinical course (CIS/RR/SP/PP)	N	2/17/2/3

2.3. TMS

Magnetic stimuli were delivered through a Magstim® Rapid^2 device (The Magstim Company Ltd, Whitland, UK, 0.5–1.4 Tesla) using a double cone coil (diameter 110 mm), highly effective in stimulating the deep cortical regions, particularly those projecting to the distal districts of the lower limbs (Terao et al., 1994). The double cone coil proved to be particularly effective in producing I1 waves, suggesting that it probably generates a more stable corticospinal volley (Terao et al., 2000). The magnetic coil was placed 2 cm behind the vertex, in a point presumed to be above the leg motor area (Terao et al., 1994). The position was marked on the scalp and the coil was maintained in the same position throughout the procedure.

After determining the motor threshold, defined as the stimulus intensity giving a MEP with an amplitude ranging from 50 to 200 μV in at least three of the 6 recording sites, we delivered stimuli 150% above the threshold. Signals were filtered (10–1000 Hz) and amplified (BrainAmp ExG MR, Brain Products GmbH). Data were examined on line and saved for subsequent analysis.

2.4. Preliminary study: strategy to reduce intra-trial MEP variability

Seven healthy volunteers (mean age 39.7, range 29–47) and 4 MS patients (mean age 38.2, range 22–48) were studied. We included also MS patients, to ensure that MEP variability and the factors influencing it did not differ between patients and normal subjects.

2.4.1. Voluntary muscle activation

Fig. 1 schematically shows the procedure we designed to obtain a predetermined degree of voluntary activation simultaneously in all tested muscles. With the subject recumbent, a 6 cm diameter round cylinder was placed under the popliteal fossa of both legs (Fig. 1A). The subject was asked to perform the following 3 movements in rapid sequence, at the same time with both legs: (1) thigh extension to lift the heels 6 cm from the bed in order to activate VM; (2) foot dorsal flexion to form a 90° angle between sole and leg in order to activate TA; (3) plantar flexion of the hallux of approximately 25°/30° in order to activate the FHB. Two simple

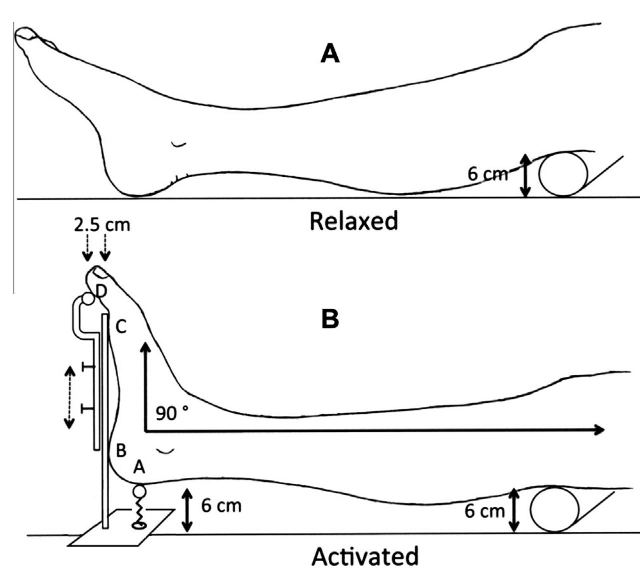

Fig. 1. Procedure of voluntary facilitation. A: relaxed position. B: simultaneous activation of vastus medialis, tibialis anterior and flexor hallucis brevis. Note that point A was designed to allow a simple skin contact, and not to support the weight of the leg.