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Repetitive spinal motor neuron discharges following single transcranial magnetic stimuli: a quantitative study

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Abstract

Objective: To quantify repetitive discharges of spinal motor neurons (repMNDs) in response to single transcranial magnetic stimuli (TMS). To assess their contribution to the size of motor evoked potentials (MEPs).
Methods: We combined the triple stimulation technique (TST) with an additional nerve stimulus in the periphery (=quadruple stimulation; QuadS). The QuadS eliminates the first action potential descending on each axon after TMS, and eliminates effects on response size induced by desynchronization of these discharges, thereby allowing a quantification of motor neurons (MNs) discharging twice. In some instances, a quintuple stimulation (QuintS) was used, to quantify the number of MNs discharging three times. Recordings were from the abductor digiti minimi of 14 healthy subjects, using two different stimulation intensities and three different levels of facilitatory muscle precontractions.
Results: The threshold to obtain repMNDs was high. Their maximal size differed markedly between subjects, ranging from 8 to 52% of all MNs. Stimulation intensity and facilitatory muscle contraction, but not resting motor threshold, correlated with the amount of repMNDs. QuintS never yielded discernible responses, hence all observed repMNDs were double discharges. RepMNDs contributed to the MEP areas, but did not influence MEP amplitudes.
Conclusions: QuadS and QuintS allow precise quantification of repMNDs. The threshold of repMNDs is high and varies considerably between subjects.
Significance: repMNDs have to be considered when MEP areas are measured. Their analysis may be of interest in neurological disorders, but standardized stimulation parameters appear essential.

Keywords: Transcranial magnetic stimulation; Motor evoked potentials; Triple stimulation technique; Collision technique

1. Introduction

After single brain stimuli, spinal motor neurons (MNs) sometimes fire not just once, but repetitively. Such repetitive spinal MN discharges (repMNDs) appear to increase with stimulation intensity and are reflected by the appearance of late components to the motor evoked potential (MEP) (Day et al., 1987; Hess et al., 1987; Di Lazzaro et al., 1998; Naka and Mills, 2000). Previous studies investigated repMNDs using a single collision technique, where a transcranial magnetic stimulus is followed by a supramaximal distal peripheral nerve stimulus (Hess et al., 1987; Berardelli et al., 1991; Naka and Mills, 2000). If appropriately timed, the antidromic action potentials ascending from the distal stimulus collide with the first descending action potential on each MN, such that only repMNDs survive and are recorded. The single collision method has disadvantages, impairing a precise quantification of repMNDs. First, action potentials evoked by brain stimuli are not synchronous, which induces phase cancellation phenomena reducing the size of the compound response in an unpredictable manner (Magistris et al., 1998; Rösler et al., 2002). Second, the recorded deflection may contain indirect components such as H-reflex or F-wave (Mazzocchio et al., 1995; Naka and Mills, 2000).

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Thus, a precise quantification of repMNDs and of their contribution to the MEP size was not possible up today.

Recently we used a triple stimulation technique (TST), which eliminates the effects of MN discharge desynchronization on the response size, allowing a quantification of the number of activated MNs (Magistris et al., 1998; 1999). In the TST recordings, repMNDs are seen, but they are eliminated from the quantification because they do not contribute to the size of the analyzed response component (Magistris and Rösler, 2003). Thus, the measured TST response size reflects only the first MN discharges occurring as a result of the brain stimulus. In the present study, we present a refined technique combining the TST with a single collision method. The quadruple stimulation (QuadS) permits an accurate quantification of repMNDs. Here, we use this technique to study the influence of facilitatory target muscle background contraction and stimulus intensity changes on the repMND response in healthy subjects. Our measurements allow a quantification of the contribution of repMNDs to the size of conventional MEPs under typical stimulation conditions.

2. Methods

2.1. Subjects

Fourteen healthy subjects participated in the study (eight men and six women). Their mean age was 24.2 years (range 22–29 years). All subjects were right-handed according to the Edinburgh Inventory of Handedness (Oldfield, 1971). The left hand was investigated in all subjects. All subjects gave written informed consent and the local ethics committee approved the experiment.

2.2. Electrophysiology

2.2.1. EMG and force recordings

A Viking Select apparatus was used for the measurements (Nicolet, Madison, Wisconsin, USA). Bandpass filters were 2 Hz to 10 kHz. Recordings were obtained from the abductor digiti minimi muscle (ADM) using the muscle belly tendon technique with silver surface electrodes (diameter 0.8 cm). A ground electrode was placed at the wrist. Subjects were comfortably seated in an armchair. Forearm, hand, and fingers II to IV were tightly strapped to a splint. The isometric voluntary contraction force of finger V abduction was measured by placing the finger on a lever attached to a force transducer (Sensotec, Inc., OH, USA.). The force signal was DC amplified using a Sedia amplifier (Sedia, Givisiez, Switzerland) and sampled at 4 kHz by a stand alone AD converter (MacLab, ADInstruments Pty Ltd., Castle Hill, NSW, Australia) connected to a personal computer (Macintosh, Apple Computer Inc., Cupertino, CA, USA). During the experiments, the force signal was displayed on the computer screen in front of the subjects, to allow visual feedback of the exerted force (Arányi et al., 1998; Rösler et al., 2002). The maximal voluntary contraction force (MVC) was measured, and the target force levels (0, 5, or 20% of MVC, see below) were indicated as goals marked on the screen.

2.2.2. Peripheral nerve stimulation

Compound muscle action potentials (CMAPs) of the ADM were recorded at rest and during a contraction of 20% MVC. The ulnar nerve was stimulated supramaximally at the wrist (yielding the $CMAP_{wrist}$). The brachial plexus was stimulated at Erb's point ($CMAP_{Erb}$), using a monopolar stimulation method described earlier (Roth and Magistris, 1987; Magistris et al., 1998). The minimal ulnar F-wave latency was measured following 16 or more wrist stimuli.

2.2.3. Transcranial magnetic stimulation

MEPs were obtained using a Magstim 200 (Magstim Company, Spring Gardens, Withland, Dyfed, UK) with a circular 90 mm hand-held coil. The intensity of the magnetic pulse was expressed as a percentage of the maximal output of 2.0 T. The center of the coil was placed over the vertex or slightly lateral toward the right hemisphere. Small displacements were made in all directions until the position yielding the lowest threshold was found. Resting motor threshold (RMT) was defined as the minimum stimulus intensity that evoked MEPs of at least 50 μV peak-to-peak amplitude in 5 or more out of 10 trials (Rothwell et al., 1999; Conforto et al., 2004). The coil was then kept in the same position throughout the experiment.

2.2.4. Triple stimulation technique

The TST is a collision method using a sequence of three stimuli to the brain, the ulnar nerve at the wrist, and the brachial plexus at Erb's point (Magistris et al., 1998; Magistris et al., 1999). The TST_{test} response is calibrated by a $TST_{control}$ response, for which the brain stimulus is replaced by a proximal nerve stimulus (succession of stimuli: Erb–wrist–Erb). The TST eliminates size influences caused by the desynchronization of transcranial magnetic stimulus (TMS) induced MN discharges, and it eliminates repMNDs from the response. Therefore, it allows quantifying the percentage of the MN pool of the target ADM that is driven to discharge by the brain stimulus (see Fig. 1(A)/(B) for a summary of the TST principle of the technique). In the present set of experiments, the timing of the three stimuli was achieved by using a dedicated software package for the Nicolet Viking apparatus obtained from Judex AS (Aalborg, DK). The delays between stimuli were calculated as follows:

- Delay I = minimal MEP latency − $CMAP_{wrist}$ latency,
- Delay II = $CMAP_{Erb}$ latency − $CMAP_{wrist}$ latency.

For the $TST_{control}$ recording, the brain stimulus was replaced by a maximal electrical stimulus to the brachial