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# A method to measure the distribution of latencies of motor evoked potentials in man

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ABSTRACT

*Objective:* To measure the intra-individual distribution of the latencies of motor evoked potentials (MepL) using transcranial magnetic stimulation.
*Methods:* We used the triple stimulation technique (TST) to quantify the proportion of excited spinal motor neurons supplying the abductor digiti minimi muscle in response to a maximal magnetic brain stimulus (Magistris et al., 1998). By systematically manipulating the TST delay, we could quantify the contribution of slow-conducting motor tract portions to the TST amplitude.
*Results:* Our method allowed the establishment of a MepL distribution for each of the 29 examined healthy subjects. MepLs of 50% of the motor tract contributing to the motor evoked potential laid between the intra-individually minimal MepL ($MepL_{min}$) and $MepL_{min}$ + 4.9 ms (range 1.6–9.2). The individual MepL distributions showed two peaks in most subjects. The first peak appeared at a MepL that was 3.0 ms longer on average (range 0.7–6.0) than $MepL_{min}$; the second peak appeared at $MepL_{min}$ + 8.1 ms on average (range 3.7–13.0).
*Conclusions:* Slow-conducting parts of the motor pathway contribute notably to the motor evoked potential. Our data suggest a bimodal distribution of central conduction times, which might possibly relate to different fibre types within the pyramidal tract.
*Significance:* We present a non-invasive method to assess slow-conducting parts of the human central motor tract.


## 1. Introduction

The central motor conduction time (CMCT) is usually assessed by the measurement of the latency of the motor evoked potential (MEP). This approach reveals only the minimal conduction time of the motor pathway, whereas the longer conduction times of slower conducting fibres remain un-assessed. However, the polyphasic muscle potentials often observed in response to transcranial magnetic stimulation (TMS) suggest that slowly conducting parts of the motor pathway may contribute prominently to the MEP.

Peripheral human motor nerve fibres were studied in detail with various electrophysiological collision methods, so that velocity distributions could be established (Kimura et al., 1978; Harayama et al., 1991). By contrast, velocity distributions of central human motor nerve fibres have not been established up to now. Conduction velocities of human pyramidal tract fibres ranging from 50 to 80 m/s were recorded during spinal surgery (Boyd et al., 1986; York, 1987; Prestor et al., 1990; Herdmann et al., 1991). Yet more comprehensive electrophysiological data on central motor conduction velocities are available from animal studies only. Single-unit recordings from pyramidal tract fibres in the cat showed that pyramidal tract cells form two populations: slowly conducting cells with conduction velocities below 21 m/s and fast conducting cells with conduction velocities of 21–90 m/s (Takahashi, 1965; Deschênes et al., 1979). Analogous pyramidal tract cell populations were found in primates (Humphrey and Corrie, 1978).

In man, only anatomical evidence indicating two distinct cell populations in the pyramidal tract is available so far. Various counts of pyramidal tract fibres all revealed a bimodal distribution of fibre diameters (Weil and Lassek, 1929; Lassek and Rasmussen, 1939; Verhaart, 1947, 1950; Graf von Keyserlingk and Schramm, 1984; Terao et al., 1994). The functional accordance of the anatomical observations with the electrophysiological data remains uncertain, as it is unreliable to predict conduction velocities of central

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nerve fibres on the basis of their diameter (Swadlow and Waxman, 1975).

Here, we present a non-invasive electrophysiological method that allows for the estimation of slow- conducting fibre portions in the human central motor tract. We combined the triple stimulation technique (TST; Magistris et al., 1998) with a collision technique originally used for investigation of the peripheral nerve system (Kimura et al., 1978; Harayama et al., 1991) and a paired pulse TMS facilitation paradigm (Kujirai et al., 1993). With this method, we established intra-individual motor conduction time distributions in 29 healthy subjects. Parts of the study were presented in preliminary form (Rösler et al., 2007; Firmin and Rösler, 2008).

## 2. Subjects and methods

### 2.1. Subjects

The study was approved by the local ethics committee. All subjects gave their written informed consent according to the Declaration of Helsinki. Twenty-nine healthy subjects volunteered to participate in the study. They were 14 males and 15 females aged 21–31 years (mean 25 years).

### 2.2. Electromyographic recordings

We used a Nicolet Viking Select apparatus (Viasys Neurocare Inc., Madison, WI, USA) for the recordings. Bandpass filters were 2 Hz to 10 kHz. Compound muscle action potentials (CMAPs) were recorded from the left abductor digiti minimi muscle (ADM) with silver surface electrodes (diameter 0.8 cm) in a belly-tendon montage.

### 2.3. Transcranial magnetic stimulation

For TMS, we used a Bistim 200 device with a maximal output of 2.0 T for each stimulator (Magstim, Whitland, Wales, UK). Magnetic pulse intensity was expressed as a percentage of the maximal output. Stimuli were applied with a circular hand held coil placed over the vertex or slightly lateral towards the right hemisphere.

A single magnetic stimulus is in many subjects insufficient to evoke a pyramidal tract impulse strong enough to excite all spinal motor neurons supplying the target muscle, depending on individual cortical excitability. Therefore, MEPs are usually facilitated by voluntary contraction of the target muscle in clinical routine (Hess et al., 1986). Yet this approach increases the probability of repetitive spinal motor neuron discharges (Z'Graggen et al., 2005), which in turn would interfere with our collision protocol described below. We had previously observed that the use of the facilitatory effect of a magnetic conditioning stimulus applied prior to the test stimulus (Kujirai et al., 1993) did not produce repetitive discharges (Magistris and Rösler, unpublished data). Therefore, we chose to take advantage of the paired pulse paradigm to facilitate the TMS response. In this protocol, a relatively weak cortical conditioning stimulus precedes a relatively strong test stimulus by some 20 ms; the response to the test stimulus is measured. We individually adjusted both, the interval between the paired stimuli (interstimulus interval; ISI) and the stimulus intensities for each subject to optimise the test response. The mean ISI was 17.6 ms (range 13–25) and stimulus intensities were 52.3% on average (range 30–80%) for the conditioning stimulus and 97.5% on average (range 85–100%) for the test stimulus. The paired pulse facilitation protocol described by Kujirai et al. (1993) uses a conditioning stimulus below resting motor threshold (RMT). However, we did not limit the stimulus intensity of the conditioning stimulus at below RMT because higher conditioning stimulus intensities yielded considerably larger motor responses in some subjects. For the purpose of this study, two objectives determined the setting of conditioning stimulus intensities: First, we needed to excite as large a proportion of the central motor tract as possible with minimal repetitive discharges because incomplete recruitment of the central motor tract introduces an excitability bias in the MEP latency (MepL) distributions. Second, we aimed at keeping the conditioning stimulus intensity as low as possible, and optimally below motor threshold in order to minimize the influence of the conditioning stimulus on synaptic transmission at spinal level and on the lower motor tract. Within this trade-off, we attached greater importance to recruiting as many central motor neurons as possible in order to minimize the excitability bias of the MepL distribution. To control for a possible influence of the conditioning stimulus on the MepL distribution, we tested 10 subjects both with and without conditioning stimulus in the same session.

MepL was defined as the shortest out of 4 trials. The minimal CMCT ($CMCT_{min}$) for each subject was calculated as follows (Rossini et al., 1985):

$$CMCT_{min} = MepL - (\text{F-wave latency} + CMAP_{wrist}\ \text{latency} - 1)/2.$$

### 2.4. Triple stimulation technique

The TST has previously been described in detail (Magistris et al., 1998). In short, it is a collision method that eliminates MEP size reduction caused by desynchronisation of TMS-induced motor neuron discharges. The method consists of a magnetic stimulus to the brain and two appropriately timed supramaximal electric stimuli to the ulnar nerve at the wrist and to the brachial plexus at Erb's point (Fig. 1A). The peripheral stimuli were applied using the two stimulators of the Nicolet Viking EMG-apparatus and were timed with a software package for the Viking apparatus obtained from Judex AS (Aalborg, DK). The delays between the stimuli were calculated as follows:

$$\text{TST delay I}(\text{brain} - \text{wrist}) = MepL_{min} - CMAP_{wrist}\ \text{latency},$$

$$\text{TST delay II}(\text{wrist} - \text{Erb}) = CMAP_{Erb}\ \text{latency} - CMAP_{wrist}\ \text{latency}.$$

The $TST_{test}$ response was compared to a $TST_{control}$ curve (Fig 1B). For the recording of the $TST_{control}$ curve, the brain stimulus was replaced by a supramaximal electrical stimulus to the brachial plexus. For the $TST_{control}$ recording, TST delays were adjusted as follows:

$$\text{TST delay I} = \text{TST delay II} = CMAP_{Erb}\ \text{latency} - CMAP_{wrist}\ \text{latency}.$$

The $TST_{control}$ recording indicates the maximal deflection of the TST curve that occurs when all peripheral motor neurons are excited. If the $TST_{test}$ amplitude equals the $TST_{control}$ amplitude, the pyramidal tract pulse evoked by TMS was sufficient to excite all peripheral motor neurons. The lower normal limit for the TST amplitude ratio ($TST_{test}$: $TST_{control}$) was 0.93 (Magistris et al., 1999).

### 2.5. Systematic delay extension: MepL distribution

If the TST delay I is extended by $\partial t$, the earliest descending action potentials escape from the first TST collision because the longer interval between TMS and the first peripheral stimulus at the wrist allows them to propagate beyond the peripheral stimulation site (Fig. 1C). The earliest action potentials on peripheral motor neurons evoking the part of the MEP with the shortest latency are therefore excluded from the TST response. This exclusion leads to an amplitude reduction ($\partial a$) of the second deflection in the TST