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# Jitter of Corticospinal Neurons During Repetitive Transcranial Magnetic Stimulation. Method and Possible Clinical Implications

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ABSTRACT

*Background:* Repetitive transcranial magnetic stimulation (rTMS) of the motor cortex activates corticospinal neurons mainly through the depolarization of cortico-cortical axons belonging to interneurons of superficial layers.
*Objective:* We used single-fiber electromyography (SFEMG) to estimate the "central jitter" of activation latency of interneural pools from one pulse of TMS to another.
*Methods:* We evaluated 10 healthy subjects and one patient with multiple sclerosis. By recording SFEMG evoked activity from the left first dorsal interosseous (FDI), we first used a standard repetitive electrical 3 Hz stimulation of the ulnar nerve at the wrist to calculate the mean consecutive difference from at least 10 different potentials. The same procedure was applied during 3 Hz repetitive TMS of the contralateral motor cortex. The corticospinal monosynaptic connection of the FDI and the selectivity of SFEMG recording physiologically justified the subtraction of the "peripheral jitter" from the whole cortico-muscular jitter, obtaining an estimation of the actual "central jitter."
*Results:* All subjects completed the study. The peripheral jitter was 28 μs ± 6 and the cortico-muscular jitter was 344 μs ± 97. The estimated central jitter was 343 ± 97 μs. In the patient the central jitter was 846 μs, a value more than twice the central jitter in healthy subjects.
*Conclusion:* Current results demonstrate that the evaluation of the central component of the cumulative cortico-muscular latency variability in healthy subjects is feasible with a minimally invasive approach. We present and discuss this methodology and provide a "proof of concept" of its potential clinical applicability in a patient with multiple sclerosis.



## Introduction

Transcranial magnetic stimulation (TMS) [1] is a tool of choice to study noninvasively the functionality of the corticospinal pathway in the intact human [2–5]. Using a near-threshold intensity of stimulation, each pulse of TMS activates corticospinal neurons trans-synaptically, through the firing of cortico-cortical axons belonging to interneurons of superficial cortical layers [6–8]. A spatio-temporal summation of their excitatory post-synaptic potentials is necessary to permit corticospinal motoneurones (MNs) to discharge. The evoked descending volleys are recordable by epidurally implanted electrodes at spinal level [repeated indirect (I)-waves at near-threshold stimulation and an early direct (D)-wave following high-intensity TMS] [9]. The temporal summation of these waves along the various corticospinal fibers impinging upon each individual spinal MN generates the related motor evoked potential (MEP), which is recordable from contralateral target muscles.

Pietro Caliandro and Simone Rossi contributed equally to this work.

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Epidural recordings provided important advances in understanding the physiology of brain activation following TMS, although they have been carried out only in patients requiring invasive therapeutic implants (i.e., mostly for chronic pain relief) or monitoring recordings during spinal neurosurgery, rather than in healthy subjects or other kind of patients. Therefore, several physiological questions still remain open: these are linked with the many possible interactions between the currents induced in the brain by TMS pulses and the complexity of cortical and/or spinal neural circuits. Indeed, these are composed, besides corticospinal output neurons, of both excitatory and inhibitory networks [10–12] including cell bodies and axons of different size, location, orientation and function [13]. Finally, differences in nervous impulse propagation along corticospinal tracts of different diameter and conduction properties should also be considered.

We aimed to investigate TMS physiology in healthy subjects with a method, applicable also in patients to get insights into corticospinal pathophysiological function. We reasoned that recording the TMS-evoked electromyographic activity by single muscle fibers, thanks to the exclusive relationship that each single muscle fiber has with a given motoneuron, might offer a better physiological window of cortical physiology than a surface recorded MEP, which includes a submaximal compound potential activity [14,15], unless complex and time-consuming collision techniques are used, as the triple stimulation technique [15].

To this aim, we developed a method combining single-fiber electromyography (SFEMG) to evaluate the neuro-muscular jitter occurring after stimulation of the peripheral nerve at 3 Hz (s-SFEMG) and the repetitive TMS (rTMS), also at 3 Hz, of the contralateral motor cortex (cortico-muscular jitter). We defined "cortico-muscular jitter" the jitter occurring after rTMS and peripheral jitter the jitter generated at the end-plate after peripheral nerve stimulation. Through the subtraction of the peripheral jitter from the whole cortico-muscular jitter, we estimated the component of the cortico-muscular jitter due to central mechanisms rather than to end-plate transmission. We used the expression "central jitter" to refer to the central component of the cumulative cortico-muscular jitter.

Previous studies have already investigated the jitter of corticospinal neurons following transcranial magnetic [16–19] and electric single-pulse stimulation [16,20,21] in healthy humans and in some patients with neurological disorders [17,18], although most of these studies used single motor unit estimation rather than SFEMG recordings [17–19,21]. They provided evidence of predominantly monosynaptic transmission of the descending volley at the spinal level, and of occurrence of jitter mainly in spinal neuron when using electric transcranial stimulation [16,20]. Moreover, Zarola and colleagues provided an elegant experimental evidence for the transsynaptic activation of corticospinal neurons following single-pulse TMS using a circular coil [16].

We originally hypothesized that jitter is taking place also following rTMS, both in healthy subjects and neurological patients. Therefore, we verified the feasibility of a new method to calculate exclusively the central component of the cortico-muscular jitter. This last issue is not negligible if we consider that end-plate transmission may account for a great variability of the cortico-muscular jitter mainly in patients with peripheral nerve damage. Here we introduce this new methodology and provide an applicative example in a patient with multiple sclerosis (MS).

## Methods

Ten healthy fully right-handed subjects (5 females, 5 males; mean age 28.5, range 23–34 years), all volunteers, naïve to the purpose of the experiment, were included after the approval of the procedure by the Ethical Committee of the participating Institutes. All were neurologically normal and denied the use of drugs or alcohol in the days preceding the experiment.

The protocol was also carried out on a patient (male, 24 years old) suffering for four years from a relapsing-remitting multiple sclerosis (MS). He was currently treated with Natalizumab at standard dose and timing (300 mg administered monthly) for two years, without side effects. His neurological examination at the time of the neurophysiological evaluation showed: nystagmus in all gaze directions and bilateral slight dysmetria; paraparetic gait (but he was able to walk without help for about 500 m) with bilateral Babinski sign; weakness in his right upper arm. Tetrahyperreflexia, prevailing in the right side, with clonus in his right lower foot. Expanded Disability Status Scale (EDSS) [22] score was 4. He also complained of severe fatigue, indexed by a score of 5 at the Fatigue Severity Scale (FSS) [23]. Upper motor function as assessed with NineHole Peg Test [24], were symmetrical (left hand: 28.5 s; right hand 26 s). At neurophysiological examinations, he had a normal central motor conduction time (measured with the standard "F-wave" method) for the left hand (6.3 ms) and a slightly increased central motor conduction time for the right hand (7.2 ms) and bilaterally for the lower limbs (19.8 ms and 20.5 ms). The magnetic resonance, which excluded gadolinium-enhanced acute brain and spinal lesions at the time of neurophysiological testing, showed multiple bilateral lesions in the subcortical white matter, in the pons in the posterior third of the corpus callosum and in the left cerebellar hemisphere.

Healthy subjects and the patient gave a written informed consent to the study, after being instructed that they could interrupt the recording session whenever they wanted. Subjects set comfortably in a reclining chair, keeping their arm fully relaxed and their hands pronated on a support providing a fully natural position.

### *Procedures of recording and peripheral stimulation*

A four-channel Synergy, Medelec electromyography version 11.1 was used for all recordings. The software for stimulated SFEMG provided by the manufacturer was used to analyze single-fiber muscle responses. A bipolar surface electrical stimulator (cathode in distal position and anode proximal, inter-electrode distance 2.2 cm) was used to stimulate the left ulnar nerve at the wrist. The stimulation producing the greatest amplitude of the conventional Compound Motor Action Potential (CMAP) recorded from the left first dorsal interosseous (FDI) muscle was first determined for each subject (silver disc electrodes of 0.99 cm in diameter were used). Filter settings were 3 Hz–10 kHz. We then used a 3 Hz repetitive nerve stimulation (RNS) with a supramaximal stimulus, 15% greater than the stimulation intensity producing the maximal CMAP amplitude and recorded from FDI by an SFEMG needle electrode. Each train of RNS was composed by 100 pulses (pulse duration was 0.1 ms).

The SFEMG needle is a specially constructed concentric needle electrode used to record action potentials in individual muscle fibers. The features of the SFEMG technique result from the small recording surface of the needle (25 microns in diameter) [25]. During SFEMG recordings, filters were set at 2 kHz (high-pass) and 10 kHz (low-pass) [26] both during electrical stimulation and rTMS. In each single subject, both during peripheral and cortical stimulation, we recorded 10 single-fiber potentials each from a different site of registration in the FDI muscle, and we analyzed at least 50 stimuli for each single-fiber. The recording sites were changed by slight movements of the needle without necessity of multiple insertions in the muscle. The criteria used for an acceptable recording were: sharp, spiky, and fast rise time; only potentials with a rise time of $<0.3$ ms and an amplitude of $>200$ μV were accepted for analysis. The jitter was measured at the rise phase of the potentials.