Reliability of Rapid TMS Stimulus-Response Curves during Tibialis Anterior Contractions on Healthy Elderly

E. Peri[1], V.M. Colombo[1], E. Ambrosini[1,2], M. van de Ruit[3], M.J. Grey[4], M. Monticone[2], A. Pedrocchi[1], G. Ferrigno[1], and S. Ferrante[1]

[1] NearLab, Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milano, Italy
[2] Physical Medicine and Rehabilitation Unit, Scientific Institute of Lissone, S. Maugeri Foundation, IRCCS, Lissone, Italy
[3] Department of Biomechanical Engineering Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, The Netherlands
[4] Neuroplasticity & Neurorehabilitation Laboratory, School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, United Kingdom

Abstract — **Transcranial Magnetic Stimulation (TMS) is a widespread technique to study corticospinal excitability. Its use in longitudinal studies is crucial to analyze the plasticity induced by rehabilitation treatments on neuromotor-impaired subjects. As TMS-related measures fluctuate with time and attention, it is crucial to collect them rapidly. Recently, it has been shown that stimulus-response (SR) curves can be acquired in less than two minutes (Mathias et al.). This technique favors the clinical use of TMS-related measures, but its inter-session reliability has not been investigated yet.**

In this study we propose a test-retest reliability analysis of five parameters extracted from SR curves acquired on the pre-activated Tibialis Anterior (TA) using the fast acquisition method. A secondary aim was to compare the reliability of these parameters for two different calculation methods of the Motor Evoked Potential (MEP) amplitude: the peak-to-peak value, referred as MEPpp, and the root mean square value, referred as MEParea. The intraclass correlation coefficients (ICC), the standard error of measurement (SEM) and the minimum detectable changes (MDC) were evaluated.

Thirteen neurologically-intact elders (age 62.2±5.1) were recruited. The acquisition protocol was set up to minimize the variability of the measurement between the two sessions, carried out on separate days: an optical tracking system was used to maintain the coil placement, the EMG data were normalized over the maximum peripherally evoked action potential and a visual feedback was displayed to the testing subject to maintain the TA activation level. All the parameters, regardless the method used to compute the MEP amplitude , showed good to excellent reliability (0.75<ICC<0.95).

Our results suggest that TMS-related measurements extracted from SR curves rapidly acquired are reliable in healthy elderly. Future studies should increase the sample size to confirm the analysis.

Keywords— **Transcranial Magnetic Stimulation, Stimulus-Response curve, inter-session reliability, healthy subjects, elderly.**

I. Introduction

Transcranial Magnetic Stimulation (TMS) is a widely used neurophysiological tool to assess the integrity of the corticospinal pathway [1]. In longitudinal studies, it can be used to assess corticospinal excitability (CSE) and, together with the fMRI [2], the neuroplasticiy in a broad number of neuro-motor diseases but some limitations occur as TMS-related measures are affected by a lot of sources of variability [3]. Indeed, the human central nervous system is constantly changing. This endogenous source of variability is not controllable and is intrinsic in TMS-related measures. Differently, a big effort in longitudinal studies involving TMS should be devoted to the control of exogenous sources of variability such as the psychophysical condition of subject, the level of muscular preactivation, the EMG electrodes positioning, and the stimulation site.

The Motor Evoked Potential (MEP) following a magnetic stimulus can be acquired both on relaxed or preactivated muscles. In the second case, the MEP is evoked for lower values of stimulation but a strict control of the level of activation is necessary [4]. Moreover, to minimize the variability due to electrode replacement on the target muscles, the MEP value is typically normalized to the maximum peripherally evoked compound motor action potential (CMAP) amplitude [4].

The MEP amplitude can be measured in two different ways: first, the peak-to-peak MEP (MEPpp), is the difference between the maximal negative and maximal positive deflection of the largest MEP; and second, the MEParea can be calculated from the root mean square value of the MEP. In the literature it has been common to use MEPpp for distal limb muscles and MEParea for proximal muscles [4,5].

The first method used to explore changes in CSE was the study of single MEPs evoked at fixed stimulus intensity [5]. This method was overcome by the acquisition of a complete

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Stimulus-Response (SR) curve including different measures of the MEP at increasing values of stimulation intensities [6]. SR curves include a higher number of information about the CSE but are time consuming for clinical purpose, as they typically require at least 10 minutes [7].

In order to minimize the time to acquire a SR curve, Mathias and colleagues [7] have recently studied the minimum Inter Stimulus Interval (ISI) at which magnetic stimuli can be delivered to upper limb muscles without affecting the CSE. Their study showed that the ISI can be reduced up to 1.4 s with no significant effect on the SR curve that were thus acquired in a shorter time (up to 2 minutes each). A detailed investigation into the reliability of this method has not yet been conducted.

Some reliability studies on TMS-related parameters have been published [3,5,6,8,9] but the methods used were not standardized: often the hotspot positioning was not controlled and the MEP was not normalized over the peripherally evoked CMAP [6,8]. Anyway, they generally assessed high intra- and inter-session reliability in healthy population for both upper and lower limbs. Among these studies, only a few have been focused on the Tibialis Anterior (TA) muscle [3,6]. This muscle is particularly interesting for clinical purpose as the dysfunctioning TA muscle is the primary cause of dropfoot, and this disorder affects a large number of neuromotor impaired subjects, preventing them from properly walking [4].

The present work aimed at analyzing the reliability of parameters extracted from SR curves acquired on the preactivated TA using the rapid method [7]. Neurologically-intact elders were involved in the study in order to make available data on an age-matched control group. The differences between results obtained with SR curves using MEPpp or MEParea were studied in order to have insight about the best method to use in longitudinal studies.

II. Methods

A. Participants and study design

Thirteen healthy individuals (6 male and 7 female), aged between 55 and 75, were enrolled in the study and provided their written informed consent. The research protocol was approved by the ethical committee of the Fondazione Salvatore Maugeri rehabilitation center.

Subjects with neurological deficits, systemic diseases, headache, cardiac pacemaker, non-dental associated metal within the cranium, history of epilepsy, musculoskeletal diseases or had sustained lower extremity injuries in the previous three months were excluded from the study.

Subjects underwent two experimental sessions in a test-retest design with 4 -7 days between sessions in order to avoid carry-over effects.

B. Experimental procedure

During each session the participant was asked to sit in a comfortable position with the dominant leg positioned with a knee angle of 100° and an ankle angle of 90°.

Before commencing SR curve acquisition a calibration procedure was required. This procedure is slightly different between the two sessions and is detailed in the following steps.

First, the TA's isometric maximum voluntary contraction (MVC) was obtained using a load cell (Tekkal, Milan, Italy).

Second, the maximal peak-to-peak amplitude of the M-wave induced by peripheral stimulation of the peroneal nerve (M_{max}) was obtained. An 8 channel electrical stimulator Rehastim (Hasomed, GmbH) was used to deliver stimuli of intensity between 0 -130 mA at a fixed pulse width (500 μs). The maximum muscular response was detected with a multi-channel EMG amplifier (Porti 32^{TM} TMSi, Netherlands) with the surface pre-gelled and self-adhesive EMG electrodes placed in a bipolar configuration as shown in Fig. 1.

Third, a magnetic stimulator Magstim Rapid^2 (Magstim, Whitland, UK) with a double-cone coil and an optical tracking system with an ad-hoc software (Polaris Vicra, Northern Digital Inc.) were used to choose the optimal positioning of the coil on the scalp (hotspot). The hotspot was defined during the first session by moving the coil in small steps around the presumed TA area in the M1. The coil position at which the minimum stimulation intensity consistently produced the largest MEP was registered as the hotspot. In the second session the same SW was used to replace the coil on the same hotspot.

Once the calibration procedure was finished, the subject was instructed to lift their toes by contracting the TA muscle maintaining 5% of the MVC. Visual feedback of exerted force was provided to facilitate a stable level of force. Whilst the subject maintained a stable contraction force, the SR curve was acquired with the stimulation intensity that varied pseudo-randomly within the limits customized on each subject in order to record both the motor threshold and the plateau. The intensity of the first stimulus was randomly chosen between the 30%MSO and the 70% MSO. The subsequent stimulus has an intensity within -5% MSO to +30% MSO of the previous stimulus. This range was chosen to avoid misfire of the stimulator when decreasing stimulation intensity [7]. During this acquisition, online visualization of the SR curves allowed minimization of the number of stimuli thereby reducing the acquisition time. Moreover, a visual feedback was provided to the operator in order to maintain the hotspot placement.

The experimental setup is reported in Figure 1.