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TRANSCRANIAL MAGNETIC STIMULATION INTENSITY AFFECTS EXERCISE-INDUCED CHANGES IN CORTICOMOTONEURONAL EXCITABILITY AND INHIBITION AND VOLUNTARY ACTIVATION

D. BACHASSON, [a,b,c*] **J. TEMESI,** [d,e] **M. GRUET,** [f] **K. YOKOYAMA,** [a,b] **T. RUPP,** [g] **G. Y. MILLET** [b,d,e†] **AND SAMUEL VERGES** [a,b†]

[a] *HP2 Laboratory, Grenoble Alpes University, F-38000 Grenoble, France*

[b] *INSERM, U1042, F-38000 Grenoble, France*

[c] *Muscle Physiology Laboratory, University of California San Diego, La Jolla, CA 92093, USA*

[d] *Laboratoire de Physiologie de l'Exercice, Université de Lyon, F-42023 Saint-Etienne, France*

[e] *Human Performance Laboratory, Faculty of Kinesiology, University of Calgary, Calgary T2N 1N4, Canada*

[f] *LAMHESS EA6312 Universities of Toulon and Nice Sophia-Antipolis, France*

[g] *Université de Savoie, Laboratoire de Physiologie de l'Exercice, F-73376 Le Bourget du Lac, France*

Abstract—Transcranial magnetic stimulation (TMS) of the motor cortex during voluntary contractions elicits electrophysiological and mechanical responses in the target muscle. The effect of different TMS intensities on exercise-induced changes in TMS-elicited variables is unknown, impairing data interpretation. This study aimed to investigate TMS intensity effects on maximal voluntary activation (VA_{TMS}), motor-evoked potentials (MEPs), and silent periods (SPs) in the quadriceps muscles before, during, and after exhaustive isometric exercise. Eleven subjects performed sets of ten 5-s submaximal isometric quadriceps contractions at 40% of maximal voluntary contraction (MVC) strength until task failure. Three different TMS intensities (I_{100}, I_{75}, I_{50}) eliciting MEPs of 53 ± 6%, 38 ± 5% and 25 ± 3% of maximal compound action potential (M_{max}) at 20% MVC were used. MEPs and SPs were assessed at both absolute (40% baseline MVC) and relative (50%, 75%, and 100% MVC) force levels. VA_{TMS} was assessed with I_{100} and I_{75}. When measured at absolute force level, MEP/M_{max} increased during exercise at I_{50}, decreased at I_{100} and remained unchanged at I_{75}. No TMS intensity effect was observed at relative force levels. At both absolute and relative force levels, SPs increased at I_{100} and remained stable at I_{75} and I_{50}. VA_{TMS} assessed at I_{75} tended to be lower than at I_{100}. TMS intensity affects exercise-induced changes in MEP/M_{max} (only when measured at absolute force level), SPs, and VA_{TMS}. These results indicate a single TMS intensity assessing maximal voluntary activation and exercise-induced changes in corticomotoneuronal excitability/inhibition may be inappropriate.

Key words: central fatigue, excitability, inhibition, exercise, motor cortex, transcranial magnetic stimulation.

INTRODUCTION

Transcranial magnetic stimulation (TMS) delivered to the primary motor cortex has permitted great progress in understanding the human motor system at rest and during fatiguing exercise (Gandevia, 2001; Di Lazzaro and Ziemann, 2013). Single-pulse TMS to the primary motor cortex elicits motor-evoked potentials (MEPs) and silent periods (SPs) in electromyography (EMG) activity during voluntary contractions of muscles controlled by the stimulated area (Di Lazzaro and Ziemann, 2013). When normalized to the maximal compound muscle action potential (M_{max}) evoked by peripheral nerve stimulation, MEPs can be used to describe changes in corticomotoneuronal excitability induced by motor activities (McNeil et al., 2013). SPs are extensively used to assess changes in GABA-mediated inhibition at the corticomotoneuronal level (Inghilleri et al., 1993; McNeil et al., 2011). Another important TMS variable is maximal voluntary activation (VA_{TMS}), a measure of the supraspinal component of the central drive i.e. the ability of the brain to maximally activate the muscles. This is calculated from the additional muscle force (i.e. superimposed twitch, SIT) elicited by TMS during submaximal to maximal voluntary contractions (MVCs) (Todd et al., 2003). This technique has been validated in a variety of muscle groups (e.g. elbow flexors (Todd et al., 2003), knee extensors (Sidhu et al., 2009), wrist extensors (Lee et al., 2008)).

*Correspondence to: D. Bachasson, Institute of Myology, Pitié-Salpêtrière Hospital, 75651 Paris Cedex 13, France. Tel: +33-6-20-26-56-69; fax: +33-1-42-16-58-81.
E-mail address: damien.bachasson@gmail.com (D. Bachasson).
† Both authors share senior authorship.

Abbreviations: EMG, electromyography; ERT, estimated resting twitch amplitude; I_{100}, 100% of the intensity to elicit MEPs of maximal amplitude at 20% MVC; I_{75}, 75% of the intensity to elicit MEPs of maximal amplitude at 20% MVC; I_{50}, 50% of the intensity to elicit MEPs of maximal amplitude at 20% MVC; MEP, motor-evoked potential; MEP_{max}, maximal MEP amplitude as determined by Boltzmann modeling; M_{max}, maximal M-wave amplitude elicited by peripheral nerve stimulation; MVC, maximal voluntary contraction; SIT, superimposed twitch; SP, silent period; TMS, transcranial magnetic stimulation; VA_{PNS}, voluntary activation assessed with peripheral nerve stimulation; Tw, twitch elicited by femoral nerve electrical stimulation in the relaxed muscle; VA_{TMS}, voluntary activation assessed with transcranial magnetic stimulation.

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One critical determinant of TMS-elicited EMG parameters is stimulus intensity. Increasing TMS intensity leads to increasing MEP amplitude and SP duration until plateaus are reached (Di Lazzaro et al., 2008). Stronger stimulus intensities can also increase antagonist muscle recruitment, resulting in the reduction of agonist muscle SIT amplitude and may therefore lead to errors when estimating VA_{TMS} (Todd et al., 2003). The force level when TMS is delivered is another important factor. Increasing the force level can initially elicit larger MEPs due to an increase in corticomotoneuronal excitability (Di Lazzaro et al., 1998). Then MEP amplitude may decrease at near-maximal force levels (i.e. high motor unit firing rates), due to the inability of some motoneurons to fire in response to TMS (Matthews, 1999; Di Lazzaro et al., 2004). Conversely, increasing force has a limited influence on SP duration (Saisanen et al., 2008).

There is no consensus for the determination of TMS intensity and different methods available (e.g. resting motor threshold, active motor threshold or stimulus–response curves at different force levels) may result in the selection of different intensities (Temesi et al., 2014a).

During fatiguing exercise, the influence of TMS intensity has only been partially investigated. Different TMS intensities may activate different populations of neurons and their behaviors may vary under different physiological conditions (e.g. nature of the fatiguing task, force level when TMS is delivered, population studied). For instance, during sustained isometric elbow flexion at constant EMG activity (corresponding to 25% of maximal EMG at baseline), McNeil et al. (2011) reported a decrease in *biceps brachii* MEP area at weak TMS intensity (i.e. eliciting MEPs of ~18% of M_{max}) while no change was observed at strong TMS intensity (i.e. eliciting MEPs of ~47% of M_{max}). After long-duration running, at relative force level (i.e. 50%, MVC) we observed increased quadriceps MEP/M_{max} at strong TMS intensity and unchanged MEP/M_{max} at weak TMS intensity (i.e. eliciting MEPs of ~37 *versus* ~51% of M_{max}, respectively) (Temesi et al., 2014b). In addition to recruiting more firing motoneurons, increasing TMS intensities should recruit more non-firing motoneurons to complete recruitment, thus differentially influencing response size as the threshold to elicit a response changes. This effect may be exacerbated or reduced due to changes in motoneuronal excitability with the practical effects on fatigue research remaining to be elucidated. The influence of TMS intensity on SITs and quantification of VA_{TMS}, during and after a fatiguing exercise is also unknown.

Due to their functional importance, the quadriceps muscles are increasingly being investigated in exercise-related studies aiming to unravel central mechanisms associated with decreased voluntary force production (Goodall et al., 2014). In such studies, it is not uncommon for a single TMS intensity to be chosen to evaluate VA_{TMS} and to demonstrate behavioral changes of the corticomotoneuronal pathway (Kalmar and Cafarelli, 2006; Goodall et al., 2010; Girard et al., 2013). In order to evaluate the implications of selecting a single all-encompassing TMS intensity, different TMS intensities were tested in the present study to evaluate MEPs, SPs, and VA_{TMS} before, during, and after exhaustive isolated quadriceps fatiguing exercise.

EXPERIMENTAL PROCEDURES

Ethical approval

This study conformed to the *Declaration of Helsinki* and was approved by the local ethics committee. All participants gave written informed consent.

Participants

Eleven healthy active men (age, 34 ± 2 years; height, 182 ± 3 cm; body mass, 77 ± 2 kg) free of contraindications to TMS (Rossi et al., 2011) were studied. Subjects were not taking any medications and were asked to refrain from alcohol, caffeine, and exercise for at least 12 h before the experiment.

Experimental set-up

Knee extensor force and EMG signals were measured as previously described (Gruet et al., 2014). Briefly, subjects sat upright with both hips and knees at 90° of flexion. Surface EMG signals were recorded from the right knee extensors (*vastus lateralis*, *vastus medialis*, *rectus femoris*) and antagonist *biceps femoris*. Signals were digitized at a sampling rate of 2000 Hz by PowerLab system (16/30—ML880/P, ADInstruments, Bella Vista, Australia) and octal bio-amplifier (ML138, ADInstruments). EMG signals were bandpass filtered (5–500 Hz) and all data were analyzed offline using Labchart 7 software (ADInstruments).

Peripheral nerve stimulation. Single electrical stimuli were delivered *via* high-voltage constant-current stimulator (modified DS7AH, Digitimer, Welwyn Garden City, UK) to the femoral nerve as previously described (Temesi et al., 2014b). The stimulus intensity (74 ± 2 mA) was set at 130% the intensity required to produce maximal M-wave (M_{max}) and twitch (Tw) amplitudes in the relaxed quadriceps to guarantee adequate assessment of central and peripheral components of neuromuscular fatigue (Neyroud et al., 2014).

TMS. Single TMS pulses were manually delivered during voluntary isometric knee extension to the contralateral motor cortex by a magnetic stimulator (Magstim 200^2, The Magstim Company Ltd., Whitland, UK) with 110-mm double-cone coil (maximum output of 1.4 T) to induce a posteroanterior current. Subjects wore a cervical collar and latex swim cap on which the optimal coil location was drawn. Every centimeter from 2 cm anterior to 2 cm posterior to the vertex at 0.5 and 1.5 cm from the nasal–inion axis over the left motor cortex, two stimuli were delivered at 70% maximal stimulator output during ~2–3 s voluntary contractions of the knee extensors at 10% MVC (Temesi et al., 2014a). Optimal coil location was defined as the site eliciting the largest mean amplitude of two MEPs in *vastus lateralis*,