

# Effects of neuromuscular electrical stimulation on contralateral quadriceps function

Thomas Cattagni, Romuald Lepers, Nicola A. Maffiuletti

#### ▶ To cite this version:

Thomas Cattagni, Romuald Lepers, Nicola A. Maffiuletti. Effects of neuromuscular electrical stimulation on contralateral quadriceps function. Journal of Electromyography and Kinesiology, 2018, 38, pp.111 - 118. 10.1016/j.jelekin.2017.11.013 . hal-01670511

## HAL Id: hal-01670511 https://u-bourgogne.hal.science/hal-01670511

Submitted on 25 Apr 2023  $\,$ 

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Effects of neuromuscular electrical stimulation on contralateral quadriceps function

Thomas Cattagni<sup>1,2</sup>, Romuald Lepers<sup>1</sup> and Nicola A. Maffiuletti<sup>3</sup>

Short title: Contralateral effect of neuromuscular electrical stimulation

<sup>1</sup>CAPS UMR1093 INSERM, Université Bourgogne Franche-Comté, Dijon, France

<sup>2</sup> Inserm Unit 1179, Team 3: Technologies and Innovative Therapies Applied to Neuromuscular diseases, UVSQ. CIC 805, Physiology-Functional Testing Ward, AP-HP, Raymond Poincaré Teaching Hospital, Garches, France.

<sup>3</sup>Human Performance Lab, Schulthess Clinic, Zurich, Switzerland

Address for reprint requests and other correspondence:

Thomas Cattagni

Hôpital Raymond Poincaré, laboratoire de la marche

104 bd Raymond Poincaré

92380, Garches

France

Email: thomas.cattagni@uvsq.fr

#### Keywords

Neuromuscular electrical stimulation; maximal voluntary contraction; voluntary activation;

EMG activity; quadriceps

#### ABSTRACT

Because maximal voluntary strength of the knee extensor muscles can be facilitated by the concomitant application of neuromuscular electrical stimulation (NMES) to the contralateral homologous muscle, we aimed to determine whether this was associated with an enhanced neural drive to the agonist muscles. A secondary goal of this study was to examine the potential dose-response relationship between NMES intensity and contralateral facilitation. Twelve healthy men (age: 30±7 yr) completed several maximal voluntary contractions (MVC) of the left knee extensors while the right quadriceps received low-intensity NMES (10% MVC), high-intensity NMES (30% MVC) or no NMES. Supramaximal paired stimuli were delivered to the left quadriceps muscle during and immediately after the MVCs to assess voluntary activation. The EMG activity of vastus lateralis (VL) and biceps femoris (BF) was recorded. MVC torque, voluntary activation and VL EMG activity were higher for both lowintensity and high-intensity NMES compared to no NMES (P<0.05), with no difference between the two NMES conditions. The acute application of NMES to the right quadriceps facilitated MVC strength of the contralateral homonymous muscle by enhancing its efferent neural drive. No evident dose-response relationship between NMES intensity and contralateral facilitation was observed.

#### INTRODUCTION

Neuromuscular electrical stimulation (NMES) is a training/rehabilitation method widely used in the fields of sport and clinical practice for its multiple effects on the neuromuscular function, at both muscular and neural levels. The acute application of NMES induces a peripheral muscle contraction while also involving the central nervous system as shown by transient increases in spinal motoneuron and cortical activity (Smith et al. 2003; Collins 2007; Bergquist et al. 2010). The chronic use of NMES can lead to muscular (e.g., hypertrophy,

changes in muscle fiber type distribution) and neural (e.g., increased neural drive) adaptations that ultimately improve maximal muscle force production (Martin et al. 1994; Maffiuletti et al. 2002; Stevens et al. 2004; Gondin et al. 2005, 2006, 2011).

Interestingly, the contralateral homologous muscles can also benefit from unilateral NMES of a specific muscle group (Hortobágyi et al. 1999; Zhou 2000; Hortobágyi and Maffiuletti 2011). Hortobágyi et al. (1999) were the first to demonstrate that 6 weeks of NMES training to the left quadriceps increased maximal knee extensor strength also on the right side (i.e., cross-education). Surprisingly, even the acute application of NMES to the right quadriceps significantly facilitated maximal voluntary strength of the left knee extensor muscles by approximately 11% (Howard and Enoka 1991). These findings, which were obtained in a heterogeneous group of untrained and active individuals, seem to prove that they were unable to generate their true maximal strength during unilateral voluntary isometric contractions, presumably because of an incomplete efferent motor outflow (neural drive). This assumption is legitimate as the knee extensors often show incomplete muscle activation during a maximal voluntary contraction (MVC) manoeuvre, as witnessed by both electromyographic (EMG) and twitch interpolation results (Rutherford et al. 1986; Hales and Gandevia 1988). Somewhat unexpectedly, however, Howard and Enoka (1991) reported that the maximal EMG activity of the left vastus lateralis (VL) muscle was basically unchanged during the administration of NMES to the right quadriceps, a result that is quite at odds with the above-discussed assumption. However, they did not assess the level of voluntary activation with the twitch interpolation technique and did not pay particular attention to EMG findings (as this was beyond the scope of their study). More specifically, they did not normalize the maximal EMG activity of the agonist muscle to the respective maximal compound muscle action potential (M wave) (so as to reduce the between-subject variability and increase the sensitivity of EMG to detect changes in activation; (Buckthorpe et al. 2012))

and did not specify whether the EMG activity of the antagonist muscles was modified by the contralateral application of NMES (an occurrence that could have altered the net knee joint torque).

Accordingly, the primary aim of this study was to re-examine whether the increase in MVC strength induced by NMES of the contralateral homologous muscles is accompanied by an enhanced neural drive to the agonist muscles (as estimated with two different techniques: surface EMG and twitch interpolation) and/or a reduced level of coactivation of the antagonist muscles. In the study of Howard and Enoka (1991), NMES was delivered exclusively at high doses (maximal tolerance), which inevitably resulted in a strong cutaneous sensation and afferent feedback. Thus, the secondary goal of this study was to examine the potential dose-response relationship between NMES current intensity and contralateral MVC strength gains. We therefore assessed MVC torque and voluntary activation of the knee extensors, as well as EMG activity of both agonist and antagonist (coactivation) muscles on the left limb while the right quadriceps received low-intensity NMES, high-intensity or no NMES. It was hypothesised that the application of NMES may play a role in increasing the efferent neural drive to the contralateral homologous muscle and that such facilitation would be proportional to NMES intensity.

#### MATERIALS AND METHODS

#### Participants

Twelve healthy men (age:  $30 \pm 7$  yr; height:  $180 \pm 6$  cm; weight:  $76 \pm 7$  kg) who were free from cardiovascular, musculoskeletal and neurological disorders volunteered to participate in the study. None of them had previous experience with NMES. Written informed consent was obtained from all participants prior to the experiments. The study protocol was

approved by the local ethics committee and conformed with the declaration of Helsinki (last modified in 2013).

#### Experimental procedure

Participants completed a single session of approximately 90 min that was arranged in two main experimental phases: (1) determination of NMES current intensities for the right quadriceps and (2) completion of several MVCs of the left knee flexors and extensors – to assess MVC torque, voluntary activation, agonist EMG activity and antagonist coactivation – while the right quadriceps received or not NMES. Participants were placed in the seated upright position with the trunk inclined at 0° with respect to the vertical and the knee joint at 109° (180°: knee fully extended) (Howard and Enoka 1991). The isometric knee joint torque was recorded using an isokinetic dynamometer (Biodex Medical System Inc., New York, USA). Participants were stabilized by means of two crossover shoulder harnesses and a belt above the abdomen. They were asked to cross their arms and to hold the shoulder straps during the entire experimental session.

During the first experimental phase (Fig. 1A), the right leg was fixed to the lever arm of the dynamometer, while the left leg was hanging free. After a standardized warm up (see below) and the completion of 2 MVCs of the right knee extensors, NMES was delivered to the right quadriceps muscle and current intensity was carefully adjusted to evoke 10% and 30% of the MVC torque (hereafter referred to as low-intensity and high-intensity NMES, respectively). We applied NMES using large electrodes and multiple current pathways because this modality is better tolerated than conventional NMES (Maffiuletti et al. 2014; Morf et al. 2015) (Fig.2). In a recent study from our laboratory (Maffiuletti et al. 2014) – in which this NMES modality was used – most of the subjects were able to tolerate NMES intensities evoking 10 and 30% of MVC torque. Therefore, also because this corresponds to

the therapeutic window range for NMES use in different clinical populations (Laufer and Snyder-Mackler 2010; Maddocks et al. 2016), in this study we arbitrarily defined low- and high-intensity NMES for evoked torque levels corresponding to 10% and 30% MVC torque, respectively. During the second experimental phase (Fig. 1A and 1B), the left leg was attached to the dynamometer lever arm and the right leg was also fixed by means of a custom-made solution. After a standardized warm up and the completion of 2 MVCs of the left knee flexors (for normalization purposes), participants were asked to perform 3 sequences of 3 MVCs (i.e., 9 trials). In each sequence, the 3 NMES conditions (low-intensity NMES, high-intensity NMES or no NMES) were randomly applied to the right quadriceps. Subjects were not informed about the NMES condition prior to each MVC. During these 9 MVC trials, voluntary activation of the left knee extensors was evaluated by means of the twitch interpolation technique, and the EMG activity of both agonist and antagonist muscles was concomitantly recorded. Four seconds before each MVC trial, a single supramaximal stimulus was delivered to evoke the maximal M wave, whose amplitude was subsequently used for normalization purposes (see below).

#### Neuromuscular electrical stimulation

NMES was delivered by means of a commercially-available multipath system (Kneehab XP, Bio-Medical Research, Galway, Ireland) that has recently been shown to generate stronger and more comfortable contractions than conventional NMES units (Maffiuletti et al. 2014). The system consists of a brace that wraps around the thigh and incorporates four large self-adhesive pre-gelled electrodes, and a battery-powered unit that delivered biphasic symmetrical square pulses lasting up to 400 µs at a frequency of 50 Hz. The on-off ratio was 5:10 s and the ramp-up and ramp-down times lasted both 1 s. During the first phase of the experiment, the experimenter progressively increased NMES current

intensity by 5-mA steps in an attempt to attain the two target torque levels of 10% (lowintensity NMES) and 30% (high-intensity NMES) MVC torque. This process was normally accomplished in 5-10 trials for low-intensity NMES and 4-8 trials for high-intensity NMES. The discomfort induced by low-intensity and high-intensity NMES was evaluated by means of a 0-10 cm horizontal visual analogue scale, where 0 indicates no discomfort and 10 indicates maximum discomfort. During the second phase of the experiment, the current intensity for low- and high-intensity NMES was set at a constant value. Right-side NMES application lasted 5 s and started simultaneously with the left-side MVC effort using manual triggering.

#### Assessment of MVC torque

Each series of MVC was consistently preceded by a standardized warm-up, which consisted of three 5-s submaximal contractions (intensity: 25, 50 and 90% of the estimated MVC torque) separated by 20 s. MVC is usually defined as a contraction in which subjects, with continuous feedback and encouragement, believe their effort to be maximal (Gandevia et al. 1996). Thus, participants were asked to contract as forcefully as possible for 4-5 s, and to build up their force progressively during 1-2 s at the beginning of the contraction. Standardized verbal encouragements were given throughout all the contractions. The 3 MVC trials within each sequence were separated by 3 min of rest to minimize the effect of fatigue and each sequence of MVCs was separated by a 5-min rest period. The torque signal was fed directly from the dynamometer into a 16-bit A/D converter (MP150, Biopac Systems, Goleta, USA) then into a computer sampling at 1 kHz using Acknowledge software (Biopac Systems).

#### Assessment of EMG activity

The EMG activity of VL, rectus femoris (RF) and biceps femoris (BF) muscles was recorded using pairs of Ag/AgCl surface electrodes (Contrôle Graphique Médical, Brie-Comte-Robert, France). The electrodes (diameter: 10 mm, inter-electrode distance: 10 mm) were applied to each muscle after careful skin preparation including shaving, abrasion with fine sandpaper and cleaning with alcohol. The electrodes were placed at a distance of 2/3between the anterior spina iliaca superior and the lateral side of the patella for the VL muscle, midway between the anterior spina iliaca superior and the superior part of the patella for the RF muscle and 1/3 along a line from the ischial tuberosity to the lateral aspect of the popliteal cavity for the BF (Hermens et al. 2000). A ground electrode was placed on the left patella. The EMG signal was sampled at 2 kHz and stored for off-line analysis with the Biopac acquisition system. Agonist EMG activity of VL and RF muscles was determined as the root mean square value over a 500-ms interval around MVC torque, and was subsequently normalized by the amplitude of the maximal M wave for respective muscles. Antagonist coactivation of the BF muscle was obtained by normalising the root mean square value recorded during knee extensors MVC with respect to the one recorded during knee flexors MVC, as a percentage (Macaluso et al. 2002; DeVito et al. 2003).

#### Assessment of voluntary activation

Voluntary activation, which is classically defined as the level of motoneuronal drive during a contraction (Gandevia et al. 1996) was evaluated using the twitch interpolation technique. Paired stimuli were delivered transcutaneously to the femoral nerve using a high-voltage (maximal voltage: 400 V) constant-current stimulator (model DS7AH modified, Digitimer, Hertfordshire, UK). The stimulus duration was 1 ms and the interval between the two paired stimuli was 10 ms (Rozand et al. 2015). The femoral nerve was stimulated using a cathode-ball electrode pressed into the femoral triangle by the same experimenter during all tests. The

anode was a large (10 x 5 cm) rectangular electrode (Compex SA, Ecublens, Switzerland) located in the gluteal fold opposite to the cathode. The optimal intensity of stimulation (i.e., ensuring full recruitment) was considered to be reached when an increase in the stimulation intensity did not induce a further increase in the amplitude of the twitch and of the concomitant M waves (Place et al. 2005). This current intensity was additionally increased by 20% to ensure stimulus supramaximality (Verges et al. 2009; Thompson et al. 2011) and kept constant throughout the session on an individual basis. Paired supramaximal stimuli were delivered during (i.e., close to MVC torque) and 4 s after the MVC to evoke respectively a superimposed and a potentiated doublet (Girard et al. 2010; Rozand et al. 2014). The level of voluntary activation was quantified by measurement of the superimposed force response to nerve stimulation during the MVC effort (Allen et al. 1995; Gandevia et al. 1996). Because the superimposed stimulation is not constantly applied at the MVC peak torque, the voluntary activation was estimated according to the following formula, including the Strojnik and Komi (1998) correction:

Voluntary activation = 
$$\left[1 - \frac{\text{superimposed doublet torque} \times (T_{\text{stim}}/\text{MVC torque})}{\text{potentiated doublet torque}} \times 100\right]$$

Where  $T_{stim}$  corresponded to the torque value at the time of the superimposed doublet.

The potentiated doublet torque was also retained as a proxy of peripheral muscle fatigue (Place et al. 2007; Rozand et al. 2015).

#### Statistical analysis

Normal distribution of data was verified using the Kolmogorov-Smirnov test. NMES current intensity levels and the corresponding self-reported discomfort scores were compared between the low- and the high-intensity NMES conditions with paired t tests. Two-factor ANOVA with repeated measures [NMES condition (no NMES, low-intensity NMES, high-

intensity NMES) x sequence order (sequence 1, sequence 2 and sequence 3)] were performed on MVC torque, voluntary activation, agonist EMG activity, potentiated doublet torque and antagonist coactivation. When a main effect or a significant interaction was found, a post-hoc analysis was made using Tukey's test. Effect sizes for each ANOVA were also calculated as partial eta squares  $(n_p^2)$ . The percent difference in MVC torque, voluntary activation and agonist EMG data between the no NMES condition and the two NMES conditions (mean of low- and high-intensity NMES) was calculated on an individual basis. The relationships between MVC torque and voluntary activation or agonist EMG activity differences were assessed using Pearson's product-moment correlations. The level of significance was set at P<0.05. All data are presented as means  $\pm$  standard deviations. Statistical analyses were performed using Statistica 10 (Statsoft, Tulsa, OK, USA).

#### RESULTS

NMES current intensity and self-reported discomfort were significantly lower for lowintensity (56  $\pm$  13 mA and 2.8  $\pm$  1.9, respectively) compared to high-intensity NMES (81  $\pm$  10 mA and 5.3  $\pm$  2.5, respectively; *P*<0.001).

For all the neuromuscular measurements, no significant interaction and no main effect of sequence order was observed (P>0.05), indicating that no fatigue occurred during the experimental session. Moreover, No main effect of NMES condition was observed for potentiated doublet torque (P>0.05), indicating no peripheral alterations in the left knee extensors following right-side NMES.

For MVC torque, the main effect of NMES condition was significant (F=6.66, P<0.01,  $n_p^2=0.38$ ). Compared to no NMES, MVC torque was significantly higher for both low-intensity (+4.4%; P<0.05) and high-intensity NMES (+5.2%; P<0.01), while no difference was observed between the two NMES conditions (Fig. 3).

For voluntary activation, the main effect of NMES condition was significant (F=11.20, P<0.001,  $n_p^2=0.51$ ). Voluntary activation was significantly higher for both lowintensity (+3.4%; P<0.05) and high-intensity NMES (+5.4%; P<0.001) compared to no NMES, while no difference was observed between the two NMES conditions (Fig. 4).

For agonist EMG activity of both VL and RF muscles, the main effect of NMES condition was significant (F=6.44, P<0.001,  $n_p^2$ =0.37). VL EMG activity was significantly higher for both low-intensity (+7.6%; P<0.05) and high-intensity NMES (+10.7%; P<0.01) compared to no NMES, while no difference was observed between the two NMES conditions (Fig. 5A). RF EMG activity was significantly higher for high-intensity NMES compared to no NMES (+9.8%; P<0.01), while no significant difference was observed between all the other conditions (Fig. 5B). For antagonist coactivation of the BF muscle, the main effect of NMES condition was significant (F=6.47, P<0.01,  $n_p^2$ =0.37). Antagonist coactivation was significantly higher for high-intensity NMES (P<0.01), while no significant difference to no NMES (P<0.01), while no significant difference was observed between all the other condition was significant (F=6.47, P<0.01,  $n_p^2$ =0.37). Antagonist coactivation was significantly higher for high-intensity NMES compared to no NMES (P<0.01), while no significant to no NMES (P<0.01), while no signific

Percent differences in MVC torque between no NMES and the two NMES conditions did not correlate significantly with voluntary activation differences (r=0.14; Fig. 7A). Conversely, as depicted in Fig. 7B, significant positive correlations were found between MVC torque and agonist EMG differences for both VL (r=0.72; P<0.01) and RF (r=0.84; P<0.001) muscles. In other words, left-side MVC torque and agonist EMG activity increased proportionally when NMES was applied to the right quadriceps.

#### DISCUSSION

The main findings of this study were that (1) the acute application of NMES to the right quadriceps significantly increased MVC torque of the left knee extensor muscles by 4-5%; (2) this was accompanied by an enhancement of both voluntary activation and agonist

EMG activity (i.e., efferent neural drive), the latter being significantly correlated to the increase in MVC torque; and (3) the NMES-mediated increase in maximal voluntary strength and neural drive basically did not differ between low-intensity and high-intensity NMES conditions.

Our current results are in agreement with the findings of Howard and Enoka (1991), and confirm that the facilitation of knee extensors MVC strength induced by concomitant NMES of the contralateral homologous muscles can be pretty consistent and substantial (range: -2 to 15% in our study and 1 to 23% in Howard and Enoka (1991)). In their study, Howard and Enoka (1991) further discriminated two groups of subjects: those presenting a bilateral facilitation (i.e., the force produced by one leg was higher during bilateral than unilateral contractions) and those presenting a bilateral deficit (i.e., the force produced by one leg was lower during bilateral than unilateral contractions). They showed that right-leg NMES resulted in a facilitation of left-leg MVC strength by 16% for the "bilateral facilitation" group and by 7% for the "bilateral deficit" group. Even if we did not assess bilateral facilitation/deficit, based on the results of Howard and Enoka (1991) we could assume that our subjects presented overall a bilateral deficit. Taken together, our results and those of Howard and Enoka (1991) prove that most healthy subjects are unable to produce their maximal strength during unilateral isometric contractions of the knee extensor muscles. Compared to that previous pioneer study (Howard and Enoka 1991) whose main focus was bilateral deficit, the present investigation additionally explored the possible effects of NMES on efferent neural drive as well as potential differences in contralateral facilitation between low- and high-intensity NMES.

Both voluntary activation and agonist EMG activity were significantly enhanced when NMES was concomitantly delivered to the contralateral muscle, and this occurred in conjunction with MVC strength facilitation. This finding is in contradiction with the results of

Howard and Enoka (1991), who reported no effect of contralateral NMES on non-normalized EMG activity of the VL muscle; however they did not give too much emphasis to these EMG findings (as this was beyond the scope of their study) and did not assess the level of voluntary activation with the twitch interpolation technique. Although the amplitude of surface EMG and the interpolated twitch torque are only crude indicators of the efferent neural drive to muscle (Farina et al. 2004), they were both modulated by NMES in a way that was indicative of increased motor unit recruitment and/or discharge rate of active motor units. The increase in EMG activity (range: -8 to 20% for VL; -6 to 26% for RF), but not in voluntary activation (range: -2 to 14%), mediated by contralateral NMES was significantly correlated with MVC strength facilitation, probably because of a greater sensitivity to change of the former. Interestingly, antagonist coactivation of the BF showed a modulation comparable to the one observed for RF (agonist) EMG, as it was significantly higher during high-intensity NMES than in the control condition. While this unexpected result did not contribute to the facilitation of MVC strength caused by NMES (as an increase in antagonist coactivation likely reduced the net knee extension torque; Baratta et al. (1988)), it was probably instigated by mechanisms comparable to those explaining agonist neural drive modulation, and discussed below.

From a biomechanical perspective, the facilitation of MVC strength and efferent neural drive caused by contralateral NMES could have been due to postural adjustments (e.g., at the hip and/or spine level) that may have differed between the two NMES conditions and the control condition (no NMES), essentially because of an actual bilateral action with NMES vs. a pure unilateral contraction without NMES. However, despite the lack of an active control condition in the present study (i.e., a voluntary contraction with a torque output matched to one of the two NMES conditions), we believe that potential condition-specific posture-related differences did not largely impact our results, as the facilitation of MVC

torque, voluntary activation and VL EMG activity was comparable between low- and highintensity NMES (which evoked respectively 10 and 30% of the MVC torque).

From a neurophysiological perspective, the facilitation of MVC strength and efferent neural drive caused by contralateral NMES could have originated from a combination of crossed excitatory effects acting at various levels of the neuraxis. Although the involvement of specific spinal and supraspinal structures in such neural integration is purely theoretical, some potential mechanisms can be discussed in relation with our findings. A hypothetical contribution of the short-latency stretch/Hoffmann reflex, i.e., an index of the balance between the excitatory and inhibitory inputs on the  $\alpha$ -motoneurons, cannot be discarded even if no crossed excitatory effects of Ia afferents are known in humans (Schieppati 1987). Indeed, muscle contractions evoked by NMES may facilitate the magnitude of the Hoffmann reflex for upper limb muscles (Hortobagyi et al. 2003). These authors assumed that the cutaneous afferent stimulations due to NMES could underlie the contralateral facilitatory effect on the Hoffmann reflex. The medium-latency crossed extension reflex, which results in flexor excitation and extensor inhibition in one limb ("withdrawing" limb) but excitation of contralateral extensors and inhibition of flexors through the involvement of group III muscle afferents (Sherrington 1910; Purves et al. 2003), could play a role in the contralateral facilitation of knee extensors we observed. Cutaneous reflexes and long-loop reflexes with the involvement of skin mechanoreceptors, free nerve endings and nociceptors (via group II and III afferents) may have contributed to the facilitation of the motoneurons innervating the contralateral homologous muscle, but their specific impact on our results is difficult to ascertain.

Despite the common misconception that NMES has a negligible impact on supraspinal structures, various functional magnetic resonance imaging studies have recently demonstrated a bilateral involvement of specific brain regions during NMES (Han et al. 2003;

Blickenstorfer et al. 2009). Similarly, based on bilateral recordings of motor evoked potentials and H reflex responses during NMES vs. voluntary contractions, Hortobágyi et al. (2003) have suggested that these two modalities of activation may have different supraspinal effects in the contralateral homologous muscle (Hortobágyi and Maffiuletti 2011). More specifically, it was conjectured that NMES is capable of modifying the excitability of interhemispheric connections and perhaps the balance between interhemispheric excitation and inhibition (Hortobágyi and Maffiuletti 2011), possibly via transcallosal mechanisms (Gueugneau et al. in press). Thus, a complex interaction of neural mechanisms may have contributed to the contralateral facilitatory effects observed in our current study, potentially as a result of a barrage of afferent inputs to the spinal cord and/or to sensorimotor cortical areas during unilateral NMES, that in turn interacted with the descending motor command.

However, contrary to expectations, the extent of afferent feedback was not a main determinant of contralateral facilitation as MVC torque, voluntary activation and VL EMG activity were equally enhanced by low- and high-intensity NMES. Thus, the balance between the amount and type of afferent feedback was probably similar between the two NMES modalities. This suggests that even low doses of NMES current, which evoked relatively weak contractions (10% MVC) and low discomfort scores (2.8 on a 0-10 scale) – and are therefore particularly relevant for clinical populations – have the potential to affect neural integration in the same manner as high-intensity NMES. Based on these results, it could also be conjectured that a sort of ceiling effect may have occurred at the higher stimulation intensity. These observations raise the interesting questions of whether (1) very low NMES currents (<10% MVC) might also induce contralateral facilitation, and (2) the actual motor response is a prerequisite for facilitation to occur. Interestingly, different sensory electrical stimulation modalities have proven effective in enhancing contralateral motor performance and neural excitability in healthy and patient populations (for a review, see Veldman et al.

(2014)), although the link with our current findings remain elusive at this stage. Similarly, the use of relatively low current intensities with wide pulse widths (the so-called wide pulse NMES) – which has recently been shown to have a major effect on ipsilateral spinal neurons and interneurons (Collins 2007; Bergquist et al. 2011) – offers an interesting perspective regarding contralateral facilitation.

This study is not without limitations. For example, the two NMES intensity levels were only determined at the beginning of the experimental phase, but we did not verify if the 10 and 30% MVC torque levels were systematically attained throughout the test session, due to technical limitations. This could explain, at least in part, the inter-individual variability in contralateral facilitation effect and the lack of difference between low- and high-intensity NMES. In our study, the application of NMES lasted only 5 s and it was repeated 9 times with 3 min of rest in-between to prevent the occurrence of muscle fatigue and/or potential "extra force". We assumed therefore that the torque evoked by NMES was constant throughout the experimental session and consistent for the two previously-determined NMES intensities. EMG activity was only recorded from RF and VL muscles, while vastus medialis activity could have provided a more complete picture of contralateral NMES effects. Another study limitation is the lack of an active control condition (e.g., submaximal voluntary contractions at 10% and 30% MVC torque) that could have been compared with NMES conditions. However, it is quite challenging to maintain a submaximal voluntary contraction at a given intensity with one leg while the other one is performing a maximal effort.

From a practical perspective, the present results have at least two important implications for muscle strength training and evaluation. First, considering the fact that nearly all individuals are unable to produce their maximal force during a unilateral isometric contraction of the knee extensor muscles, low-intensity NMES can be delivered to the contralateral homologous muscle during maximal strength testing in an attempt to maximize

efferent neural drive and performance while circumventing the use of unfriendly techniques ipsilaterally (such as the twitch interpolation). The facilitatory effects observed in this study remain nevertheless to be confirmed (1) for muscles other than the knee extensors, (2) in dynamic (and possibly functionally-relevant) actions, (3) in women and (4) in patient populations with muscle weakness and voluntary activation deficits due to aging, neurological and orthopedic conditions (Yue et al. 1999; Stackhouse et al. 2001; Berth et al. 2002; Mizner et al. 2003; Stevens et al. 2003a, 2003b). Second, considering the well-known cross education effect induced by unilateral NMES training (Hortobágyi et al. 1999) – when the contralateral muscle is stimulated while the ipsilateral one is not contracted – it is likely that a training/rehabilitation modality consisting of contralateral low-intensity NMES during MVC of the ipsilateral homologous muscle would be beneficial to improve muscle strength and restore voluntary activation deficits through a chronic facilitation effect.

#### CONCLUSION

The present study provided evidence that the acute application of NMES to the contralateral quadriceps, even with low current intensities, significantly facilitated maximal voluntary strength of the ipsilateral knee extensor muscles by enhancing its efferent neural drive. A complex combination of spinal and supraspinal adjustments mediated by contralateral NMES likely contributed to the facilitation of the motoneurons innervating the contralateral homologous muscle.

#### REFERENCES

Allen GM, Gandevia SC, McKenzie DK. Reliability of measurements of muscle strength and voluntary activation using twitch interpolation. Muscle Nerve. 1995 Jun;18(6):593–600.
Baratta R, Solomonow M, Zhou BH, Letson D, Chuinard R, D'Ambrosia R. Muscular

coactivation. The role of the antagonist musculature in maintaining knee stability. Am J Sport Med. 1988/03/01. 1988;16(2):113–22.

- Bergquist AJ, Clair JM, Collins DF. Motor unit recruitment when neuromuscular electrical stimulation is applied over a nerve trunk compared with a muscle belly: triceps surae. J Appl Physiol. 2010 Dec 23;110(3):627–37.
- Bergquist AJ, Clair JM, Lagerquist O, Mang CS, Okuma Y, Collins DF. Neuromuscular electrical stimulation: implications of the electrically evoked sensory volley. Eur J Appl Physiol. Springer-Verlag; 2011 Oct 30;111(10):2409–26.
- Berth A, Urbach D, Awiszus F. Improvement of voluntary quadriceps muscle activation after total knee arthroplasty. Arch Phys Med Rehabil. 2002 Oct;83(10):1432–6.
- Blickenstorfer A, Kleiser R, Keller T, Keisker B, Meyer M, Riener R, et al. Cortical and subcortical correlates of functional electrical stimulation of wrist extensor and flexor muscles revealed by fMRI. Hum Brain Mapp. 2009 Mar;30(3):963–75.
- Buckthorpe MW, Hannah R, Pain TG, Folland JP. Reliability of neuromuscular measurements during explosive isometric contractions, with special reference to electromyography normalization techniques. Muscle Nerve. 2012 Oct;46(4):566–76.
- Collins DF. Central Contributions to Contractions Evoked by Tetanic Neuromuscular Electrical Stimulation. Exerc Sport Sci Rev. 2007 Jul;35(3):102–9.
- DeVito G, McHugh D, Macaluso A, Riches PE. Is the coactivation of biceps femoris during isometric knee extension affected by adiposity in healthy young humans? J Electromyogr Kinesiol. Elsevier; 2003 Oct;13(5):425–31.
- Farina D, Merletti R, Enoka RM. The extraction of neural strategies from the surface EMG. J Appl Physiol. 2004;96(4).
- Gandevia SC, Allen GM, Butler JE, Taylor JL. Supraspinal factors in human muscle fatigue: evidence for suboptimal output from the motor cortex. J Physiol. 1996 Jan 15;490 (Pt

2:529–36.

- Girard O, Micallef J-P, Noual J, Millet GP. Alteration of neuromuscular function in squash. J Sci Med Sport. 2010 Jan;13(1):172–7.
- Gondin J, Brocca L, Bellinzona E, D'Antona G, Maffiuletti NA, Miotti D, et al. Neuromuscular electrical stimulation training induces atypical adaptations of the human skeletal muscle phenotype: a functional and proteomic analysis. J Appl Physiol. 2011 Feb 1;110(2):433–50.
- Gondin J, Duclay J, Martin A. Soleus- and gastrocnemii-evoked V-wave responses increase after neuromuscular electrical stimulation training. J Neurophysiol. 2006;95(6):3328–35.
- Gondin J, Guette M, Ballay Y, Martin A. Electromyostimulation training effects on neural drive and muscle architecture. Med Sci Sports Exerc. 2005 Aug;37(8):1291–9.
- Gueugneau N, Grosprêtre S, Stapley PJ, Lepers R. High-frequency neuromuscular electrical stimulation modulates interhemispheric inhibition in healthy Humans. J Neurophysiol. 2016;
- Hales JP, Gandevia SC. Assessment of maximal voluntary contraction with twitch interpolation: an instrument to measure twitch responses. J Neurosci Methods. 1988/09/01. 1988;25(2):97–102.
- Han BS, Jang SH, Chang Y, Byun WM, Lim SK, Kang DS. Functional magnetic resonance image finding of cortical activation by neuromuscular electrical stimulation on wrist extensor muscles. Am J Phys Med Rehabil. 2003 Jan;82(1):17–20.
- Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. J Electromyogr Kinesiol. 2000;10(5):361–74.
- Hortobágyi T, Maffiuletti NA. Neural adaptations to electrical stimulation strength training. Eur J Appl Physiol. 2011 Oct;111(10):2439–49.

- Hortobágyi T, Scott K, Lambert J, Hamilton G, Tracy J. Cross-education of muscle strength is greater with stimulated than voluntary contractions. Motor Control. 1999 Apr;3(2):205–19.
- Hortobagyi T, Taylor JL, Petersen NT, Russell G, Gandevia SC. Changes in segmental and motor cortical output with contralateral muscle contractions and altered sensory inputs in humans. J Neurophysiol. 2003/10/10. 2003;90(4):2451–9.
- Howard JD, Enoka RM. Maximum bilateral contractions are modified by neurally mediated interlimb effects. J Appl Physiol. 1991 Jan 1;70(1):306–16.
- Laufer Y, Snyder-Mackler L. Response of Male and Female Subjects After Total Knee Arthroplasty to Repeated Neuromuscular Electrical Stimulation of the Quadriceps Femoris Muscle. Am J Phys Med Rehabil, 2010 Jun;89(6):464–72.
- Macaluso A, Nimmo MA, Foster JE, Cockburn M, McMillan NC, De Vito G. Contractile muscle volume and agonist-antagonist coactivation account for differences in torque between young and older women. Muscle Nerve. 2002/07/13. 2002;25(6):858–63.
- Maddocks M, Nolan CM, Man WD-C, Polkey MI, Hart N, Gao W, et al. Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: a randomised double-blind, placebo-controlled trial. Lancet Respir Med. 2016 Jan;4(1):27–36.
- Maffiuletti NA, Pensini M, Martin A. Activation of human plantar flexor muscles increases after electromyostimulation training. J Appl Physiol. 2002;92(4).
- Maffiuletti NA, Vivodtzev I, Minetto MA, Place N. A new paradigm of neuromuscular electrical stimulation for the quadriceps femoris muscle. Eur J Appl Physiol. 2014 Jun;114(6):1197–205.
- Martin L, Cometti G, Pousson M, Morlon B. The influence of electrostimulation on mechanical and morphological characteristics of the triceps surae. J Sports Sci. 1994

Aug;12(4):377-81.

- Mizner RL, Stevens JE, Snyder-Mackler L. Voluntary activation and decreased force production of the quadriceps femoris muscle after total knee arthroplasty. Phys Ther. 2003 Apr;83(4):359–65.
- Morf C, Wellauer V, Casartelli NC, Maffiuletti NA. Acute Effects of Multipath Electrical Stimulation in Patients With Total Knee Arthroplasty. Arch Phys Med Rehabil. 2015 Mar;96(3):498–504.
- Place N, Maffiuletti NA, Ballay Y, Lepers R. Twitch potentiation is greater after a fatiguing submaximal isometric contraction performed at short vs. long quadriceps muscle length. J Appl Physiol. 2005;98(2):429–36.
- Place N, Maffiuletti NA, Martin A, Lepers R. Assessment of the reliability of central and peripheral fatigue after sustained maximal voluntary contraction of the quadriceps muscle. Muscle Nerve. 2007 Apr;35(4):486–95.
- Purves D, Augustine GJ, Fitzpatrick D, Katz LC, LaMantia A-S, McNamara JO, et al. Neuroscience. Third. Sinauer Associates; 2003.
- Rozand V, Cattagni T, Theurel J, Martin A, Lepers R. Neuromuscular fatigue following isometric contractions with similar torque time integral. Int J Sports Med. 2015 Jan;36(1):35–40.
- Rozand V, Pageaux B, Marcora SM, Papaxanthis C, Lepers R. Does mental exertion alter maximal muscle activation? Front Hum Neurosci. Frontiers; 2014 Jan 26;8:755.
- Rutherford OM, Jones DA, Newham DJ. Clinical and experimental application of the percutaneous twitch superimposition technique for the study of human muscle activation.J Neurol Neurosurg Psychiatry. 1986/11/01. 1986;49(11):1288–91.
- Schieppati M. The Hoffmann reflex: a means of assessing spinal reflex excitability and its descending control in man. Prog Neurobiol. 1987;28(4):345–76.

- Sherrington CS. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. J Physiol. Wiley-Blackwell; 1910 Apr 26;40(1–2):28–121.
- Smith G V, Alon G, Roys SR, Gullapalli RP. Functional MRI determination of a doseresponse relationship to lower extremity neuromuscular electrical stimulation in healthy subjects. Exp brain Res. 2003 May;150(1):33–9.
- Stackhouse SK, Stevens JE, Lee SC, Pearce KM, Snyder-Mackler L, Binder-Macleod SA. Maximum voluntary activation in nonfatigued and fatigued muscle of young and elderly individuals. Phys Ther. 2001/04/26. 2001;81(5):1102–9.
- Stevens JE, Mizner RL, Snyder-Mackler L. Quadriceps strength and volitional activation before and after total knee arthroplasty for osteoarthritis. J Orthop Res. 2003a Sep;21(5):775–9.
- Stevens JE, Mizner RL, Snyder-Mackler L. Neuromuscular Electrical Stimulation for Quadriceps Muscle Strengthening After Bilateral Total Knee Arthroplasty: A Case Series. J Orthop Sport Phys Ther. 2004 Jan;34(1):21–9.
- Stevens JE, Stackhouse SK, Binder-Macleod SA, Snyder-Mackler L. Are voluntary muscle activation deficits in older adults meaningful? Muscle Nerve. 2003/01/01. 2003b;27(1):99–101.
- Strojnik V, Komi P V. Neuromuscular fatigue after maximal stretch-shortening cycle exercise. J Appl Physiol. 1998 Jan 1;84(1):344–50.
- Thompson CK, Lewek MD, Jayaraman A, Hornby TG. Central excitability contributes to supramaximal volitional contractions in human incomplete spinal cord injury. J Physiol. 2011 Aug 1;589(Pt 15):3739–52.
- Veldman MP, Maffiuletti NA, Hallett M, Zijdewind I, Hortobágyi T. Direct and crossed effects of somatosensory stimulation on neuronal excitability and motor performance in humans. Neurosci Biobehav Rev. 2014 Nov;47:22–35.

- Verges S, Maffiuletti NA, Kerherve H, Decorte N, Wuyam B, Millet GY. Comparison of electrical and magnetic stimulations to assess quadriceps muscle function. J Appl Physiol. 2009 Feb 1;106(2):701–10.
- Yue GH, Ranganathan VK, Siemionow V, Liu JZ, Sahgal V. Older adults exhibit a reduced ability to fully activate their biceps brachii muscle. J Gerontol A Biol Sci Med Sci. 1999/06/11. 1999;54(5):M249-53.
- Zhou S. Chronic neural adaptations to unilateral exercise: mechanisms of cross education. Exerc Sport Sci Rev. 2000 Oct;28(4):177–84.

23

#### **Figure legends**

**Fig. 1.** Graphical overview of the experimental design. (A) represents the right-leg knee extension efforts required to define the two NMES intensity levels of 10% (low-intensity NMES) and 30% (high-intensity NMES) of the MVC. (B) represents the left-leg knee flexion efforts performed to determine the maximal EMG activity of the antagonist muscle. (C) represents the left-leg knee extension efforts performed to compare MVC torque, voluntary activation, agonist EMG activity and antagonist coactivation across the three following conditions: no NMES, low-intensity NMES and high-intensity NMES of the contralateral (right) homologous muscles. Arrows indicate the timing of paired stimuli delivered during and after each MVC. NMES: neuromuscular electrical stimulation; MVC: maximal voluntary contraction. The 3 MVC trials within each sequence were separated by 3 min of rest and each sequence of MVCs was separated by a 5-min rest period.

**Fig. 2.** Electrode positions for NMES (right thigh) and EMG recordings of vastus lateralis and rectus femoris (left thigh).

Fig. 3. Left-leg MVC torque recorded while the right quadriceps received no NMES, low- and high-intensity NMES. Circles represent individual data. \*significantly higher than no NMES (P < 0.05).

**Fig. 4.** Left-leg voluntary activation recorded while the right quadriceps received no NMES, low- and high-intensity NMES. Circles represent individual data. \*significantly higher than no NMES (P<0.05).

**Fig. 5.** Left-leg EMG activity of agonist muscles (A: vastus lateralis; B: rectus femoris) recorded while the right quadriceps received no NMES, low- and high-intensity NMES. Circles represent individual data. \*significantly higher than no NMES (P<0.05).

**Fig. 6.** Left-leg antagonist coactivation of the BF muscle recorded while the right quadriceps received no NMES, low- and high-intensity NMES. Circles represent individual data. \*significantly higher than no NMES (P<0.05).

**Fig. 7.** Scatterplots showing the relationship between MVC torque and voluntary activation (A) or maximal EMG activity (B) differences between no NMES and the two NMES conditions. The linear regression equation in (A) is y=4.26+0.13x (r=0.14; P=0.65). The linear regression equations in (B) are y=1.24+0.41x (r=0.72; P<0.01) for VL and y=1.61+0.42x (r=0.84; P<0.001) for RF.

C















**Thomas Cattagni** is in post-doctoral position at the Inserm Unit 1179, Team 3: Technologies and Innovative Therapies Applied to Neuromuscular diseases, UVSQ and at the CIC 805, Physiology-Functional Testing Ward, AP-HP, Raymond Poincaré Teaching Hospital, Garches, France. He received the Ph.D. degree in Sport Science in 2014 from the University of Burgundy in Dijon, France. His research mainly focuses on the aging of the neuromuscular system.

**Romuald Lepers** is a professor in the National Institute for Health and Medical Research at the Burgundy University in Dijon - France. He earned a Ph.D. in Biomechanics and Exercise Physiology from the University of Paris XI in France. His research focuses on neuromuscular mechanisms of human fatigue during prolonged exercises. He is a member of the French Society of Sport Sciences.

**Nicola A. Maffiuletti** was born in Bergamo, Italy, in 1973. He received the Ph.D. degree in Sport Science in 2000 from the University of Burgundy in Dijon, France. He has been an Assistant Professor in the same University since 2001, and is currently Director of the Human Performance Lab at the Schulthess Clinic in Zurich, Switzerland. His current research interests include the exploration of neuromuscular function in orthopaedic patients and the clinical implementation of neuromuscular electrical stimulation. He is a fellow of the European College of Sport Science and a member of the International Society of Electrophysiology and Kinesiology.

CCEN