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ABSTRACT

Purpose: The training effects of neuromuscular electrical stimulation (NMES) delivered with narrow pulses are relatively well known. Wide-pulse NMES has recently received increasing attention, but mainly for acute applications. The aim of the present study was to investigate the effect of NMES training with narrow vs. wide pulses on isometric strength and on the underlying neuromuscular adaptations. **Methods:** Thirty-six healthy men were randomly allocated to a control group and two NMES training groups (narrow-pulse group, NG and wide-pulse group, WG). Trained participants completed a 6-week NMES program, followed by a 6-week detraining period. NMES with narrow (0.2 ms) or wide (1 ms) pulses was applied to the quadriceps at a stimulation frequency of 50 Hz and at maximal tolerable current intensity. All participants completed three testing sessions: before (PRE) and after (POST) training, as well as after the detraining period (DE). Measurements included ultrasonography, maximal voluntary contractions (MVC) with the twitch interpolation technique, transcranial magnetic and peripheral nerve stimulations. **Results:** MVC torque increased significantly and similarly for the two NMES training groups, from PRE-to-POST (11% and 12% for NG and WG, respectively) and PRE-to-DE (12% and 7% for NG and WG, respectively). This was associated with significant and similar increases of voluntary activation, evoked doublet torque and muscle thickness in both groups. A significant cross education effect was also observed for both groups (8% and 10% for NG and WG, respectively). No changes in corticospinal responsiveness were observed. **Conclusions:** Despite differences in total applied current, narrow- and wide-pulse NMES training induced similar isometric strength gains, neural and muscular adaptations in healthy men, likely due to a comparable level of evoked torque throughout the training programs. **Key Words:** NMES TRAINING, DETRAINING, VOLUNTARY ACTIVATION, CROSS-EDUCATION; HYPERTROPHY

INTRODUCTION

Neuromuscular electrical stimulation (NMES) training programs have been shown to improve knee extension and plantar flexion maximal voluntary contraction (MVC) strength by 10-20% in healthy subjects [see Gondin et al. (1) for a review], due to a combination of neural and muscular adaptations. Neural adaptations have been evidenced by an increase in voluntary activation (assessed through twitch interpolation and EMG techniques) of the stimulated muscle (2-6) and also by the so-called cross education effect (i.e. increased strength of the contralateral non-trained muscle) (7, 8), mainly after relatively short training programs (< 4 weeks). Muscular adaptations, which have been predominantly observed following programs longer than 4 weeks, include increased muscle mass of the stimulated muscle with the associated architectural changes (2, 9, 10), but without changes in twitch contractile properties (2, 6, 11). In terms of strength gains, NMES training effectiveness is related to the level of tension/force generated by NMES (i.e. as a percentage of MVC) (12-14), which justifies why NMES is usually delivered at relatively high current intensities, i.e. close to maximal tolerable intensity (15).

Because of the limitations of high-intensity NMES, such as fatigability and discomfort that may preclude its effectiveness and acceptability (16), NMES with wider pulses than those used conventionally (≥ 1 ms) has increasingly been studied in the last 20 years [see Bastos et al. (17) for a review]. Delivered with low current intensities ($\leq 10\%$ of MVC), wide-pulse NMES is known to favor afferent involvement with reflexive motor unit recruitment and generation of central torque [see Collins (18) and Bergquist et al. (19) for reviews]. Yet, it failed to improve plantar flexor strength following nine sessions of wide-pulse NMES training over three weeks (20). Even if this form of NMES has been less studied, wide-pulse NMES delivered close to maximal tolerable intensity has been shown to evoke similar knee extension forces, but using lower current intensity,

than narrow pulses throughout a typical NMES session (21). Therefore, the use of wide-pulse NMES allows to overcome practical issues associated with maximal stimulator output attainment, which is frequent with narrow pulses in both training and clinical settings (22, 23). To the best of our knowledge, only two studies conducted with healthy older adults (24) and people with multiple sclerosis (25) investigated the effectiveness of a high-intensity wide-pulse NMES training program. Both studies found similar plantar flexor/dorsiflexor strength gains and mobility improvements compared to narrow-pulse NMES, which however remain to be confirmed in young healthy populations, while further comparing the level of evoked force and the nature of the adaptations between the two NMES conditions.

The aim of this study was to compare the effect of a 6-week NMES training program with narrow vs. wide pulses on knee extension isometric strength, as well as on the underlying neural and muscular adaptations in healthy participants. We hypothesized similar isometric strength gains and adaptations (i.e., increased voluntary activation, cross-education effect and increased muscle thickness) for the two NMES modalities, mainly due to the expected comparable levels of evoked force.

MATERIALS & METHODS

Participants

Forty-two healthy men were included in the study after medical examination. They were fully informed of the procedure and gave written consent to participate in this study. All of them were recreationally active (self-reported physical activity) and reported no history of neurological or musculoskeletal impairment. None of them had previously engaged in NMES training. Participants were asked to refrain from strenuous and unaccustomed physical activity for 24 h

before testing. The study protocol was approved by the local ethics committee (CPP SUD-EST I), registered at ClinicalTrials.gov (#NCT04857710) and conducted in accordance with the latest update of the Helsinki Declaration.

Five participants did not wish to participate in the study after the familiarization visits and another participant dropped out of the study after five training sessions due to personal reasons. Thirty-six participants were ultimately included in the study and randomly assigned to the different groups, yet two participants missed the last testing session (i.e. after detraining). All of them completed the three NMES familiarization sessions, and all of the participants in the training groups (i.e. NG and WG) completed the 18 NMES training sessions. Participants' main characteristics are shown in Table 1.

Experimental design

The experimental design is illustrated in Figure 1A. Three familiarization visits aimed to accommodate the participants with neuromuscular testing and NMES, as recommended before initiating a NMES training program (26). Thereafter, all participants completed three experimental testing sessions that were conducted approximately at the same time of the day (± 51 min). Testing sessions consisted of neuromuscular assessments including ultrasound measurements, MVC with the twitch interpolation technique, transcranial magnetic stimulation and peripheral nerve stimulation during submaximal contractions at 20% of MVC (Figure 1B). After a pretraining test session (PRE), participants were randomly assigned to either the control group, the narrow-pulse group (NG) or the wide-pulse group (WG). Participants in the training groups completed a 6-week NMES program targeting the right quadriceps, for a total of eighteen sessions conducted at the laboratory under the supervision of an investigator trained to use the NMES system. NG and WG

participants were retested after 6 weeks of NMES training (POST) and again after 6 weeks of usual activity (detraining, DE). Control group participants were asked not to change their usual activities for the duration of the study, and were tested at baseline (PRE), after 6 weeks (POST) and again after 6 weeks (DE) to assess the reliability of the neuromuscular assessments.

Neuromuscular testing

Torque recordings. Knee extension torque was measured during voluntary and evoked contractions using an isometric dynamometer (ARS dynamometry; SP2 Ltd., Ljubljana, Slovenia). Participants were seated with the hips and knees at 90° and 60° of flexion (with 0° referring to the extended neutral position), respectively. The leg was attached to the chair by a noncompliant strap proximal to the intermalleolar axis. Trunk and pelvis were also securely strapped to the chair to prevent compensatory movements. After a standardized warm-up of ten submaximal isometric contractions (duration: 3-5 s) at increasing intensities until reaching 90% of the perceived maximal strength, right-side (trained) knee extensor torque was assessed during a MVC without stimulation. Subsequently, two MVCs were performed with femoral nerve stimulation (100-Hz paired pulses, see “*Peripheral nerve stimulation*” section) delivered as close as possible to the highest MVC torque and ~2 s following the MVC in the relaxed and potentiated state. During the MVC, participants were instructed to contract their knee extensors as hard as possible for ~4 s with a progressive torque build-up, and strong verbal encouragements and visual feedback were consistently provided. A 1-min resting period separated each MVC, and additional trials were performed if the MVC torque still increased at the last MVC or if the difference between the two highest MVCs was > 5%. After transcranial magnetic stimulations (see “*Transcranial magnetic stimulation*” section), three MVCs were also performed on the left (untrained) side, yet without

femoral nerve stimulation, to assess a potential cross-education effect of NMES training. The knee extension torque signal was low-pass filtered (20 Hz) and analog-to-digital converted at a sampling rate of 2 kHz by a PowerLab system (16/35; ADInstruments, Bella Vista, Australia).

EMG recordings. EMG signals from the right vastus lateralis were recorded during neuromuscular testing with pairs of self-adhesive surface electrodes (Melitracen 100; Covidien, Mansfield, MA) in bipolar configuration. Pairs of electrodes were placed on the muscle belly of the vastus lateralis following SENIAM recommendations (27), with an interelectrode (center-to-center) distance of 30 mm, and a reference electrode placed on the ipsilateral patella. Before electrode placement, the skin was shaved, abraded, and cleaned with isopropyl alcohol to limit impedance. EMG signals were amplified with an octal bio-amplifier (ML138; ADInstruments), band-pass filtered (5–500 Hz), and analog-to-digital converted at a sampling rate of 2 kHz by the PowerLab system.

Peripheral nerve stimulation. Rectangular electrical pulses of 1 ms (400-V maximal output voltage) were delivered via a constant-current stimulator (DS7R, Digitimer, Hertfordshire, UK) to the right femoral nerve. A 30-mm diameter surface cathode (Meditrace 100) and a 50 × 100 mm anode (Durastick Plus, DJO Global, Vista, CA) were taped to the skin overlying the femoral triangle and the gluteal fold, respectively. To determine the optimal intensity of stimulation, single electrical pulses were first delivered at 50 mA and then the intensity was increased in 10-mA increments until knee extension peak twitch torque and vastus lateralis M-wave responses plateaued. The resulting stimulation intensity was then increased by 30% to account for activity-induced changes in axonal responsiveness. Single pulses were used to induce maximal M-waves

at rest and during contractions at 20% MVC, whereas paired pulses delivered at 100 Hz were used to measure voluntary activation and doublet torque.

Transcranial magnetic stimulation. Single magnetic pulses were delivered to the left motor cortex via a concave double-cone coil (110-mm diameter, maximum output 1.4 T) oriented to induce a posterior-to-anterior cortical current and powered by a monopulse stimulator (Magstim 200², TheMagstim Company, Whitland, UK). Coil placement was manually controlled by the same investigator throughout all testing sessions. Optimal transcranial magnetic stimulation location was established for each visit as the position that elicited the largest motor evoked potential (MEP) of the vastus lateralis during a low-level voluntary contraction (20% MVC). The optimal position was marked on a swim cap secured to the scalp. Then, active motor threshold was determined as the stimulation intensity that elicited a MEP in two out of three stimulations during a 20% MVC knee extension. Stimulation intensity was increased in 5% steps from 20% of maximal stimulator output until a consistent MEP amplitude was found. Thereafter, stimulus intensity was reduced in 1% steps until the lowest intensity to elicit a MEP was found. MEPs were evoked at 120% of active motor threshold during ten consecutive ~3-s contractions at 20% MVC separated by rest periods of 10 s.

Ultrasound measurements. To localize the measurement sites over the quadriceps muscle group, an anthropometric tape measure was placed along the length of the thigh from the superior border of the patella to the anterior superior iliac spine. The thickness of vastus medialis was measured at 20% (distal) of this distance, and the thickness of vastus lateralis, vastus intermedius and rectus femoris at 50% of this distance. These locations correspond to the maximum cross-sectional area

of each individual quadriceps muscle (28, 29). To account for the medial location of vastus medialis, measurements were taken at 12.5% of thigh circumference in the medial direction from the midpoint of the thigh. To account for the lateral location of vastus lateralis, measurements were taken from the lateral thigh (10% of thigh circumference in the lateral direction). These measurement points were marked with a pen (Figure 2A).

With the participant lying supine, ultrasound measurements were performed with a diagnostic ultrasound system (Aplio XG SSA-790A, Toshiba, Tokyo, Japan) by placing a 6.2-12 MHz linear transducer (PLT-805AT, Toshiba) over each of the measurement sites. The images were taken by an investigator trained to the use of real-time ultrasound. The depth of the image was adjusted until the femur was visible in the centre of the screen, and the gain was adjusted until muscle boundaries were also visible. Three longitudinal images (i.e., taken lengthwise of muscle belly) were captured for each measuring site and saved for subsequent analysis. Sufficient ultrasound gel was used to minimise muscle compression with the transducer head.

Neuromuscular electrical stimulation

NMES familiarization. Familiarization visits encompassed a progressive number of NMES-evoked contractions (i.e. 10, 15 and 20 contractions for session 1, 2 and 3, respectively) using the same set up and NMES characteristics as for the NMES training programs (described below).

NMES training. The training program consisted of eighteen 20-min sessions of NMES distributed over a 6-week period, with a progressive number of sessions per week (i.e. 2 sessions/week during the two first weeks, 3 sessions/week during the two following weeks, and 4 sessions/week during the last two weeks). This program distribution was chosen to respect the progressive overload concept which is a fundamental principle in strength training (30). The schedule of training

sessions was individually designed in accordance to each participant's availabilities while spacing out sessions by at least 24 h. Each training session consisted of 30 NMES trains of 10 s delivered to the right quadriceps and interspersed by rest periods of 30 s (10 s ON / 30 s OFF; duty cycle = 25%). Two 2-mm-thick self-adhesive electrodes were placed over the anterior aspect of the thigh. One electrode, measuring 198 cm² (180 × 110 mm, axion GmbH, Leonberg, Germany), was placed on the distal third of thigh length. The other electrode, measuring 85 cm² (125 × 86 mm, axion GmbH), was placed 5-7 cm below the inguinal ligament. The current was delivered with a custom-made NMES system (31), which can provide symmetrical biphasic rectangular pulses up to 180 mA. For NG, narrow pulses (0.2 ms) were applied at a frequency of 50 Hz, whereas wide-pulses (1 ms) were applied at a frequency of 50 Hz for WG. Each train included a 2-s ramp-up, a 7-s steady stimulation and a 1-s ramp-down, to improve comfort and avoid a sudden jolt. Current intensity was monitored online and was gradually increased throughout the training session by the participants themselves to a level of maximally tolerated intensity. The evoked torque was also recorded during all training sessions with the same dynamometer used for testing (see "*Torque recordings*" part).

Data analysis

Voluntary and evoked torque. MVC torque was determined as the highest voluntary torque attained during the three MVCs. Superimposed and resting doublet torque and voluntary activation were measured from the trial with the highest MVC torque, as follows (32):

Voluntary activation = $[1 - \text{superimposed doublet torque} \times (\text{torque at stimulation} / \text{maximal torque before stimulation}) / \text{doublet torque}] \times 100$

Maximal evoked torque (MET) for each NMES-induced contraction was defined as the highest torque reached during each train. Mean MET (i.e. the mean MET of all contractions of a NMES session) was calculated for each familiarization and training session and was expressed as a percentage of MVC torque measured at PRE.

EMG. Maximal M-wave peak-to-peak amplitude was measured during brief voluntary contractions at 20% MVC. MEP peak-to-peak amplitude was also measured, averaged and expressed as a percentage of maximal M-wave.

Muscle thickness. Muscle thickness was measured with the calliper tool of the ultrasound system by an investigator who was totally blinded to participants identity and group randomization. Muscle thickness of vastus medialis and vastus intermedius was defined as the distance between the superficial aponeurosis and the most superficial aspect of the femur. Thickness of vastus lateralis and rectus femoris muscles was defined as the distance between the superficial and the deep aponeurosis (28) (Figure 2B). Muscle thickness was quantified in the middle, left and right portion of each image (33) and was determined for each muscle as the average of the three measurement sites (middle, left, right) and the three images. Quadriceps muscle thickness was expressed as the average of vastus lateralis, vastus medialis, vastus intermedius and rectus femoris thicknesses.

Statistical analysis

Statistical analyses were performed with R [R Core Team (2021)] and JAMOVİ software (version 1.1.9; <https://www.jamovi.org/download.html>). Shapiro-Wilk and Levene tests were used to examine data normality and homogeneity of variance, respectively. All data are presented as mean values \pm standard deviations. Statistical significance was set at $p < 0.05$.

For CG, one-way repeated measures ANOVAs were performed to compare neuromuscular variables obtained at PRE, POST and DE. A one-way ANOVA was done to compare MET of the three NMES familiarization sessions between all groups. Unpaired Student's t-test were conducted to compare MET, current intensity and current charge of the 18 NMES training sessions between the training groups (NG, WG). A mixed-model ANOVA with session as within-participant factor and group as between-participant factor, was used to compare the evolution of mean MET during both NMES familiarization and training. Mixed-model ANOVAs with time (PRE, POST, DE) as within-participant factor and group (NG, WG) as between-participant factor were performed for all neuromuscular variables (i.e. MVC torque, voluntary activation, MEP, muscle thickness and doublet torque) to analyse training and detraining effects for each group. Tukey post hoc tests were performed when the ANOVAs revealed a significant effect or an interaction. When a main effect of time was observed without any interaction with the group, unpaired Student t-tests or Mann-Whitney U tests were conducted to compare PRE-to-POST or PRE-to-DE changes between groups. When significance was attained, effect sizes were presented as partial eta-squared (η^2p), with values ≥ 0.1 , ≥ 0.25 and ≥ 0.4 representing small, medium and large effects, respectively. Linear regression model was also developed to explain the variance in MVC torque gains after NMES training. The model included changes in voluntary activation, contralateral MVC torque, doublet torque and quadriceps thickness, as well as MET of the 18 NMES training sessions, as

independent variables. Pearson correlation coefficients were also specifically calculated between PRE-to-POST changes in MVC torque and respective changes in voluntary activation.

As two participants did not complete the neuromuscular testing session at DE, mixed-model ANOVAs for neuromuscular variables were performed on 25 participants with imputation of missing data, as well as on 23 participants by excluding the two individuals with missing data. As the results were basically identical, we chose to present the data and analyses from the 25 participants. Data was imputed using the R-package “*Mice*” and a prediction matrix including “time” and “group”. Two thousand imputations were used with a fixed seed for reproducibility and to minimize simulation error (34). Data was assumed to not be missing at random.

RESULTS

NMES training

Concerning NMES familiarization, MET of the three sessions did not differ between CG, NG and WG (31.6 ± 13.8 , 28.0 ± 11.5 and $28.7 \pm 13.4\%$ MVC, respectively; $p = 0.78$). There was a main effect of session ($p = 0.001$; $\eta^2_p = 0.29$) for mean MET, but no main effect of group ($p = 0.86$) nor a session \times group interaction ($p = 0.90$). Mean MET was higher for the third familiarization session as compared to the first ($p < 0.001$) and the second ($p = 0.01$) sessions, with no difference between the first two sessions ($p = 0.09$). Mean current intensity was 53 ± 24 , 54 ± 23 and 53 ± 22 mA for the first session, and 72 ± 22 , 65 ± 17 and 60 ± 19 mA for the third session, for CG, NG and WG respectively.

Concerning NMES training, there was no significant difference between NG and WG for MET of the 18 sessions (47.9 ± 14.1 and $57.4 \pm 12.5\%$ MVC, respectively; $p = 0.09$) (Figure 3A). Mean current intensity was 121 ± 33 and 85 ± 24 mA ($p = 0.004$; $d = 1.27$), and mean charge was

1.2 ± 0.3 and 4.2 ± 1.2 mC ($p < 0.001$; $d = 3.47$) throughout the NMES training program in NG and WG, respectively. There was a main effect of session for mean MET ($p < 0.001$; $\eta^2_p = 0.54$), but no main effect of group ($p = 0.09$), nor a session \times group interaction ($p = 0.67$). Mean MET increased progressively during the first seven sessions and then plateaued from the eighth session until the end of the training program for both groups (Figure 3B). Mean current intensity was 101 ± 27 and 64 ± 19 mA for the first session, 128 ± 42 and 89 ± 30 mA for the eighth session, and 130 ± 40 and 96 ± 33 mA for the last session, for NG and WG respectively.

Changes in isometric strength, voluntary activation, evoked force and muscle thickness

Neuromuscular variables for CG are presented in the Supplemental Digital Content (Supplemental Table 1, Supplemental Digital Content). There was no time effect for any neuromuscular variable for CG (all $p \geq 0.10$).

MVC torque. There was a main time effect for MVC torque ($p < 0.001$; $\eta^2_p = 0.49$), but no main group effect, nor a time \times group interaction ($p = 0.54$ and $p = 0.39$, respectively). MVC torque was higher at POST ($p < 0.001$) and DE ($p < 0.001$) compared to PRE, with no difference between POST and DE ($p = 0.42$) (Figure 4A). Mean PRE-to-POST increases in MVC torque were not significantly different between NG and WG ($10.8 \pm 6.7\%$ and $12.4 \pm 9.2\%$, respectively; $p = 0.63$) (Figure 5A).

There was a main time effect for contralateral MVC torque ($p < 0.001$; $\eta^2_p = 0.38$), but no main group effect, nor a time \times group interaction ($p = 0.77$ and $p = 0.56$, respectively). Contralateral MVC torque was higher at POST ($p < 0.001$) and DE ($p < 0.001$) compared to PRE, with no difference between POST and DE ($p = 0.98$) (Figure 4B). Mean PRE-to-POST increases

in contralateral MVC torque were not significantly different between NG and WG ($7.7 \pm 8.4\%$ and $9.6 \pm 10.0\%$, respectively; $p = 0.61$) (Figure 5A).

Neural and muscular variables. There was no main effect of group ($p \geq 0.13$) nor a time \times group interaction ($p \geq 0.51$) for any neural and muscular variable. There was a main time effect for voluntary activation ($p = 0.001$; $\eta^2_p = 0.26$). Voluntary activation was higher at POST ($p = 0.005$) but not at DE ($p = 0.10$) compared to PRE, with no difference between POST and DE ($p = 0.10$) (Figure 6A). Mean PRE-to-POST increases in voluntary activation were not significantly different between NG and WG ($3.6 \pm 6.3\%$ and $6.7 \pm 8.5\%$, respectively; $p = 0.31$) (Figure 5A). There was no main time effect ($p = 0.90$) for MEP (15.0 ± 5.1 , 16.7 ± 4.5 and $16.2 \pm 6.9\%$ of maximal M-wave for NG, and 13.6 ± 7.4 , 13.0 ± 6.1 and $12.7 \pm 4.7\%$ of maximal M-wave for WG, at PRE, POST and DE, respectively).

Concerning muscular variables, there was a main time effect for doublet torque ($p < 0.001$; $\eta^2_p = 0.36$) and quadriceps thickness ($p < 0.001$; $\eta^2_p = 0.36$). Doublet torque was not different at POST compared to PRE ($p = 0.61$), but was higher at DE compared to both PRE ($p < 0.001$) and POST ($p = 0.006$) (Figure 6B). Mean PRE-to-DE increases in doublet torque were not significantly different between NG and WG ($11.2 \pm 14.3\%$ and $7.3 \pm 8.4\%$, respectively; $p = 0.27$) (Figure 5B). Quadriceps thickness was higher at POST than PRE ($p < 0.001$) but lower at DE than POST ($p = 0.013$) (Figure 6C). Mean PRE-to-POST increases in quadriceps thickness were not significantly different between NG and WG ($5.6 \pm 4.6\%$ and $4.5 \pm 5.7\%$, respectively; $p = 0.63$) (Figure 6A). Data of the four separate quadriceps heads (vastus lateralis, vastus medialis, rectus femoris and vastus intermedius) are presented in the Supplemental Digital Content (Supplemental Table 2, Supplemental Digital Content). There was a main time effect for thickness of vastus lateralis ($p <$

0.001; $\eta^2p = 0.62$), vastus medialis ($p = 0.007$; $\eta^2p = 0.19$) and rectus femoris ($p < 0.001$; $\eta^2p = 0.57$) muscles, but not for vastus intermedius ($p = 0.22$).

Multivariate model predicting MVC torque gains

The linear regression model including all independent variables explained 46% of the variance of MVC torque gains after 6 weeks of NMES training (adjusted $R^2 = 0.46$; $p = 0.004$). The results displayed that changes in voluntary activation were the strongest predictor of MVC torque gains ($p < 0.001$; $\eta^2p = 0.50$) (Figure 7), while contralateral MVC torque ($p = 0.189$), doublet torque ($p = 0.330$) and quadriceps thickness ($p = 0.598$) changes, as well as MET of the 18 NMES sessions ($p = 0.480$) did not significantly contribute to the model. The explanation of the variance of MVC torque gains raised to 48% (adjusted $R^2 = 0.48$; $p < 0.001$) with a linear model including only neural variables (voluntary activation and contralateral MVC torque changes).

DISCUSSION

The main aim of the present study was to compare the effect of a 6-week NMES training program with narrow vs. wide pulses on maximal knee extension isometric strength and on the underlying neural and muscular adaptations. We also looked at the persistent effect after a detraining period. MVC torque and contralateral MVC torque (i.e. cross-education) increased after both NMES training programs to a similar extent, and these changes persisted at the end of the detraining period. Strength gains were accompanied by comparable neural and muscular adaptations for the two NMES modalities, as evidenced by the significant increases in voluntary activation and quadriceps muscle thickness. These findings could be potentially ascribed to the

similar level of evoked torque, although the total applied current differed throughout the two training programs.

Narrow- vs. wide-pulse NMES training

At the end of the familiarization sessions, the level of evoked torque was not different between the two training groups (28% vs. 29% MVC, respectively) suggesting similar tolerance to NMES. In this context and throughout the 18 sessions of the NMES training programs, evoked torque level did not differ significantly ($p = 0.085$, despite a moderate effect size: $d = 0.72$) between narrow- and wide-pulse NMES (approximately 48% and 57% MVC for NG and WG, respectively), which confirms our previous observations during a single NMES session (approximately 35% and 38% MVC for narrow- and wide-pulse NMES, respectively) (21). As a result, we observed similar effectiveness of wide-pulse NMES on maximal strength compared to conventional NMES (i.e. NG). Nevertheless, the mean current charge was greater for wide- than narrow-pulse NMES (around 4.2 and 1.2 mC for WG and NG, respectively), yet the mean current intensity was higher for narrow-pulse NMES compared to wide-pulse NMES (approximately 121 and 85 mA for NG and WG, respectively). The maximal stimulator output (180 mA) was attained in one third (34%) of the narrow-pulse NMES sessions (compared to only 6% for wide-pulse NMES), which could have induced suboptimal levels of evoked torque and therefore minimized narrow-pulse NMES training effectiveness. This effect could have been even more pronounced with several commercially-available stimulators, whose maximal output is 100-120 mA. As fewer issues with maximal stimulator output limitations were encountered with wide-pulse compared to narrow-pulse NMES of the quadriceps, while providing similar effects, the use of wide-pulse

NMES should be recommended in some specific conditions requiring high NMES training levels (such as with athletes or patients accustomed to the discomfort induced by NMES) (35).

Isometric strength gains

Narrow-pulse NMES training led to 11% MVC torque gains that persisted after 6 weeks of detraining, in line with previous NMES studies of similar duration (36-38). To the best of our knowledge, the present study is the first to investigate the effects of wide-pulse NMES training applied at maximal tolerable intensity on the quadriceps muscle. Indeed, whereas Neyroud et al. (20) investigated the effects of 3 weeks of wide-pulse NMES of the triceps surae muscle, stimulation intensity was set to evoke contractions of only 5% of MVC torque in order to favor the development of extra torque through reflex pathways [see Bergquist et al. (19) for a review], which unsurprisingly did not improve strength. In the present study, applying wide-pulse NMES to the quadriceps at maximal tolerable intensity led to 12% MVC torque gains, which were comparable in magnitude to those observed after narrow-pulse NMES training, and also similarly persisted after detraining. The similarity in isometric strength gains between narrow- and wide-pulse NMES training is potentially attributable to the comparable level of evoked torque throughout respective training programs. Indeed, the dose-response relationship between evoked torque level (i.e. NMES training intensity) and strength gains is well established (1, 12, 14). The present results confirm previous findings from studies having compared narrow- and wide-pulse NMES training applied during voluntary contractions. For instance, narrow- and wide-pulse NMES were shown to be equally effective in improving plantar flexor strength by 17% in older adults (24) and by 39% in people with multiple sclerosis (25). However, both studies did not specifically focus on the comparison between NMES modalities. The inclusion of a sham NMES

condition, in addition to the control group, would have definitively ruled out a potential placebo effect.

Neural adaptations

Strength gains induced by NMES training have usually been ascribed to neural adaptations as evidenced by increased voluntary activation (2, 3, 6), cross-education effect (7, 8) and decreased antagonist coactivation (4). In the present study, the level of voluntary activation and contralateral MVC torque increased similarly after the two NMES training programs. Moreover, consistent with the relatively short duration of the training intervention, changes in voluntary activation were the strongest predictor of strength gains induced by the 6-weeks NMES training programs. These neural adaptations suggest a training-induced improvement of motor unit recruitment and/or discharge rate for the stimulated muscle group (39), both potentially mediated by changes in the descending cortical outflow. Yet, these adaptations do not seem to be attributable to increased corticospinal responsiveness, as NMES training did not modify MEP amplitude in the present study. Similar results have been observed after 4 and 8 weeks of unilateral strength training (40), as well as local vibration training (41). Since voluntary activation informs about maximal descending cortical outflow during MVCs, the measurement of MEPs during submaximal contractions (20% MVC in the present study) might be questioned as our results do not rule out the possibility that corticospinal responsiveness could have changed during MVCs. Furthermore, there is a lack of consistency in the results of studies that assessed the effects of strength training on MEPs at rest or during weak contraction, suggesting that if training changes corticospinal responsiveness, then the changes may be too subtle to be detected with transcranial magnetic stimulations [see Carroll et al. (42) and Kidgell and Pearce (43) for reviews]. Moreover, we

recently reported that a single session of NMES applied to the quadriceps at the maximal tolerable current intensity did not modify any marker of central nervous system responsiveness (i.e. spinal reflex, thoracic motor evoked potential and MEP) (21). Despite the selective activation of afferent pathways and the supposed involvement of the central nervous system with wide pulses, especially at low current intensities (18), neural adaptations were comparable after narrow- and wide-pulse NMES training in our study. This could be explained by the use of high current intensities that could have offset the acute neural adjustments observed elsewhere at low current intensity (44). As such, the antidromic collision in motor axons associated to high-intensity NMES could have limited/prevented the orthodromic transmission of the afferent volley in the current study (19, 45).

The evidence for a preservation of neural adaptations after detraining appears less clear in the present study. Persistence of voluntary activation improvement is for instance equivocal, as voluntary activation increased from PRE-to-POST while PRE to-DE and POST-to-DE changes were not significant. If we consider this result as a lack of persistence of neural adaptations, this would be in accordance with previous findings obtained after NMES training (3) and voluntary resistance training (46, 47). However, the persistence of cross education at the end of the detraining period may suggest that neural changes were actually relatively long-lasting, as already reported following NMES training (6) or voluntary resistance training (48, 49). The time course of neural changes after NMES training – regardless of pulse duration – remains to be carefully investigated, as a potential persistence of neural adaptations seems essential in clinical populations.

Muscular adaptations

As for neural adaptations, training-induced muscular changes were similar after narrow- and wide-pulse NMES training, probably due to comparable NMES training intensities. Indeed,

we found that quadriceps muscle thickness increased similarly at the end of the two NMES training programs (approximately 5%) and then decreased after the detraining period. As ultrasonography has been demonstrated to be a valid and reliable tool to investigate training-induced muscle hypertrophy (50), we conclude that 6 weeks of NMES increased the amount of contractile tissue, likely as a result of the anabolic and myogenic responses induced by each single NMES session (51). Increases in myofiber size [assessed with muscle biopsies (11, 52, 53)] and quadriceps muscle volume [measured with magnetic resonance imaging (9, 10) or ultrasonography (2)] have already been reported after NMES training. As an example, a 4.9% increase in quadriceps muscle volume (as assessed through magnetic resonance imaging) has recently been observed after 8 weeks of NMES training (54). In the present study, the global hypertrophy of the quadriceps masked some differences between superficial (vastus lateralis, vastus medialis and rectus femoris) and deep (vastus intermedius) muscle heads. The lack of changes in vastus intermedius muscle thickness suggests a lower involvement of the only non-superficial quadriceps muscle portion with NMES. In turn, this corroborates the superficial and incomplete recruitment pattern imposed by NMES (55), despite the application of maximal tolerable current intensity. However, this finding partially contrasts with those of Akagi et al. (54) who reported a significant increase in muscle volume of all quadriceps muscles (including vastus intermedius), yet the relative increase being smaller for the VI. Additionally, Gondin et al. (2) showed similar increases in cross-sectional area for the three vastii muscles, but no changes for the rectus femoris muscle after 8 weeks of conventional NMES training (2). Different NMES settings, especially electrodes placement, might influence the spatial recruitment of muscle fibers (56, 57) and therefore contribute to explain these discrepancies between studies.

We observed comparable increases of doublet torque after the detraining period, but not immediately after NMES training, in NG and WG. Improved knee extensor muscle contractility – though delayed – has already been reported after NMES training (6). The apparent dissociation between NMES-induced hypertrophy and unchanged contractile properties after training has also been already observed (3, 54), and could be explained by the submaximal contractile responses associated with twitches or doublets. For example, Duchateau and Hainaut (58) showed similar increases in MVC and maximal tetanic torque without changes in twitch contractile properties after 6 weeks of NMES training. The delayed increase in doublet torque observed here could have been caused by transient and moderate contractile failure in the first days after the end of the training programs, that has already been observed following NMES training (6). This could be due to lingering muscle damage that was potentially resolved after the detraining period, as muscular alterations are mainly involved in acute NMES-induced force production impairments (21). Delayed adaptations of musculotendinous elastic structures involved in force transmission (e.g. tendon, sarcolemma) could also potentially explain these late changes in muscle contractility.

CONCLUSIONS

NMES training with wide pulses induced similar knee extensor isometric strength gains as narrow-pulse NMES, likely due to a comparable level of evoked torque for the two modalities. Isometric strength gains were accompanied by neural (i.e. increased voluntary activation and cross-education effect) and muscular adaptations (i.e. hypertrophy), that were also comparable between NMES training programs. The potential transfer of these isometric strength gains and neuromuscular adaptations to more functional outcomes such as explosive and isokinetic strength, jumping performance and fatigability remains to be demonstrated.

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ACCEPTED

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FIGURE LEGENDS

Figure 1. Experimental design (A) and neuromuscular testing (B). NMES, neuromuscular electrical stimulation; NG, narrow-pulse group; WG, wide-pulse group; MVC, maximal voluntary contraction; PNS, peripheral nerve stimulation; TMS, transcranial magnetic stimulation.

Figure 2. Ultrasound measurement sites over the quadriceps muscle group (A), and a representative ultrasound image of the vastus lateralis with thickness measurements between the superficial and deep aponeuroses (B). RF, rectus femoris; VI, vastus intermedius; VL, vastus lateralis; VM, vastus medialis.

Figure 3. Mean maximal evoked torque (MET) of the 18 NMES training sessions (panel A) and evolution of mean MET throughout the NMES program (panel B) for narrow-pulse (NG; red) and wide-pulse (WG; blue) groups. Data are mean and SD. Significantly lower than consecutive sessions (###, $p < 0.001$).

Figure 4. Maximal voluntary contraction (MVC) torque (panel A) and contralateral MVC torque (panel B) for narrow-pulse (NG; red) and wide-pulse (WG; blue) groups before (PRE) and after (POST) NMES training, as well as after detraining (DE). For panel A and B, circles, error bars and small circles indicate mean, SD and individual data, respectively. Significantly higher than PRE (***, $p < 0.001$).

Figure 5. PRE-to-POST (panel A) and PRE-to-DE (panel B) changes in maximal voluntary contraction (MVC) torque, voluntary activation, contralateral MVC torque, doublet torque and quadriceps thickness for narrow-pulse (NG, red) and wide-pulse (WG, blue) groups.

Figure 6. Voluntary activation (panel A), doublet torque (panel B) and quadriceps thickness (panel C) for narrow-pulse (NG; red) and wide-pulse (WG; blue) groups before (PRE) and after (POST) NMES training, as well as after detraining (DE). Circles, error bars and small circles indicate mean, SD and individual data, respectively. Significantly higher than PRE (***, $p < 0.001$; **, $p < 0.01$). Significantly different than POST (††, $p < 0.01$; †, $p < 0.05$).

Figure 7. Correlation between PRE-to-POST changes in maximal voluntary contraction (MVC) torque and PRE-to-POST changes in voluntary activation for narrow-pulse (NG; red) and wide-pulse (WG; blue) groups pooled together. The 95% confidence interval is shown around the linear trend line.

SUPPLEMENTAL DIGITAL CONTENT

SDC 1: Supplemental Digital Content.docx

Figure 1

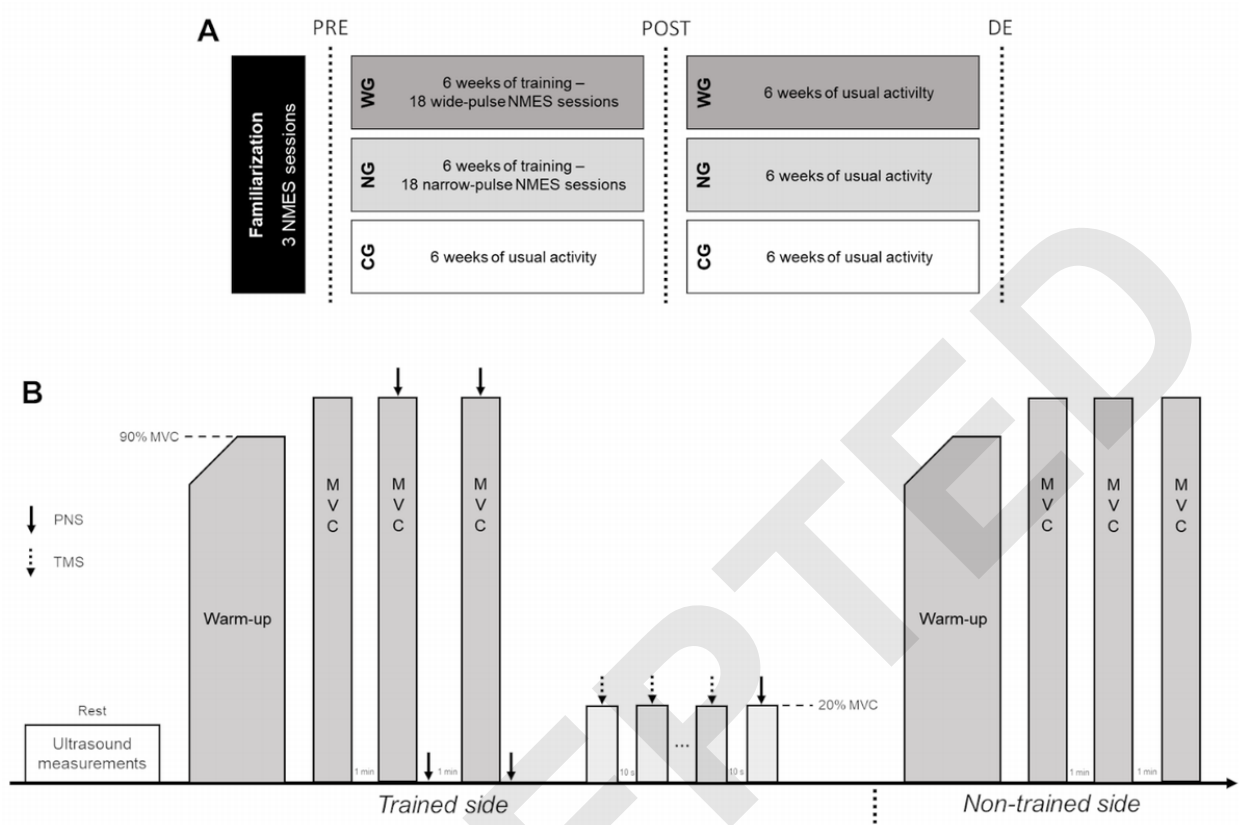


Figure 2

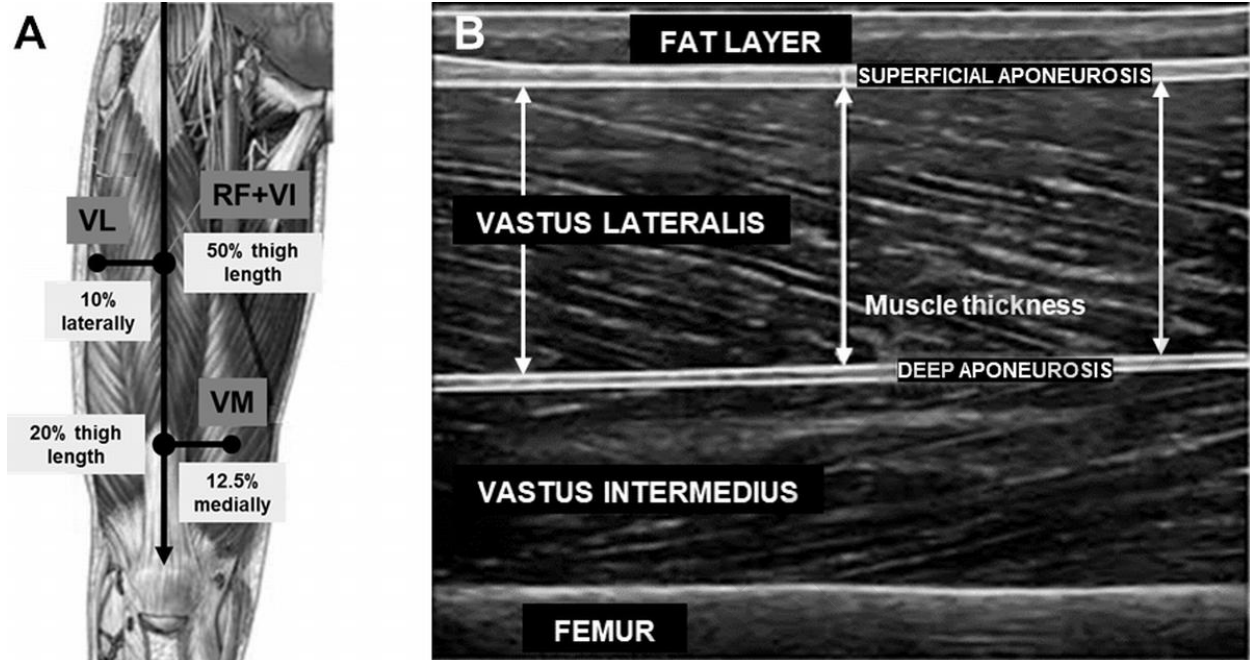


Figure 3

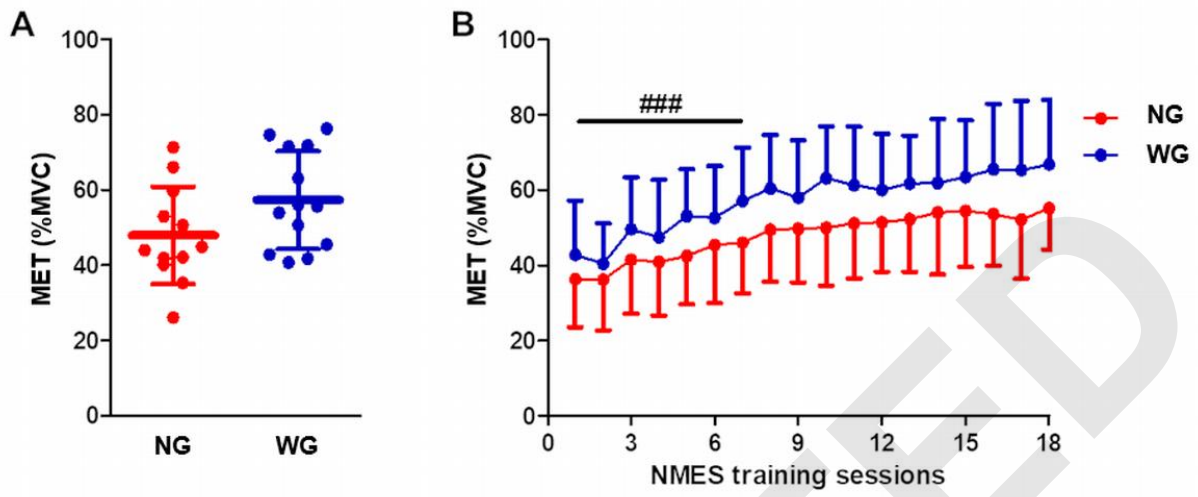


Figure 4

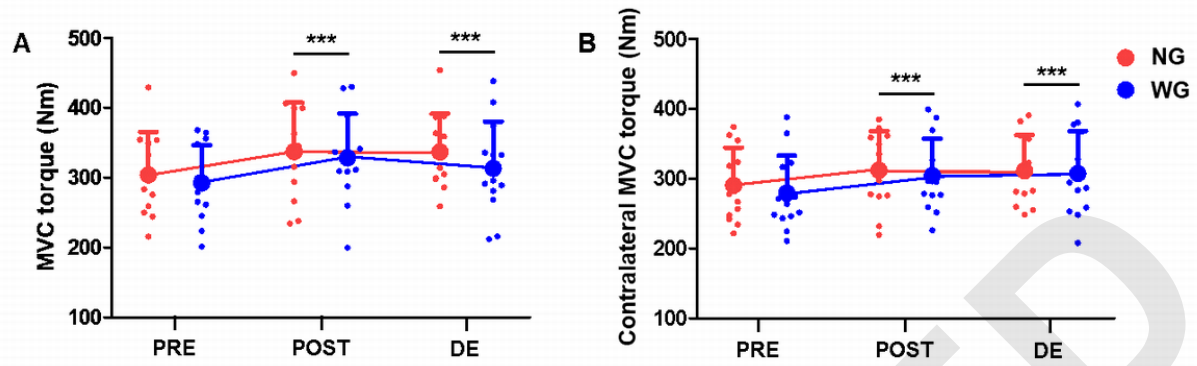


Figure 5

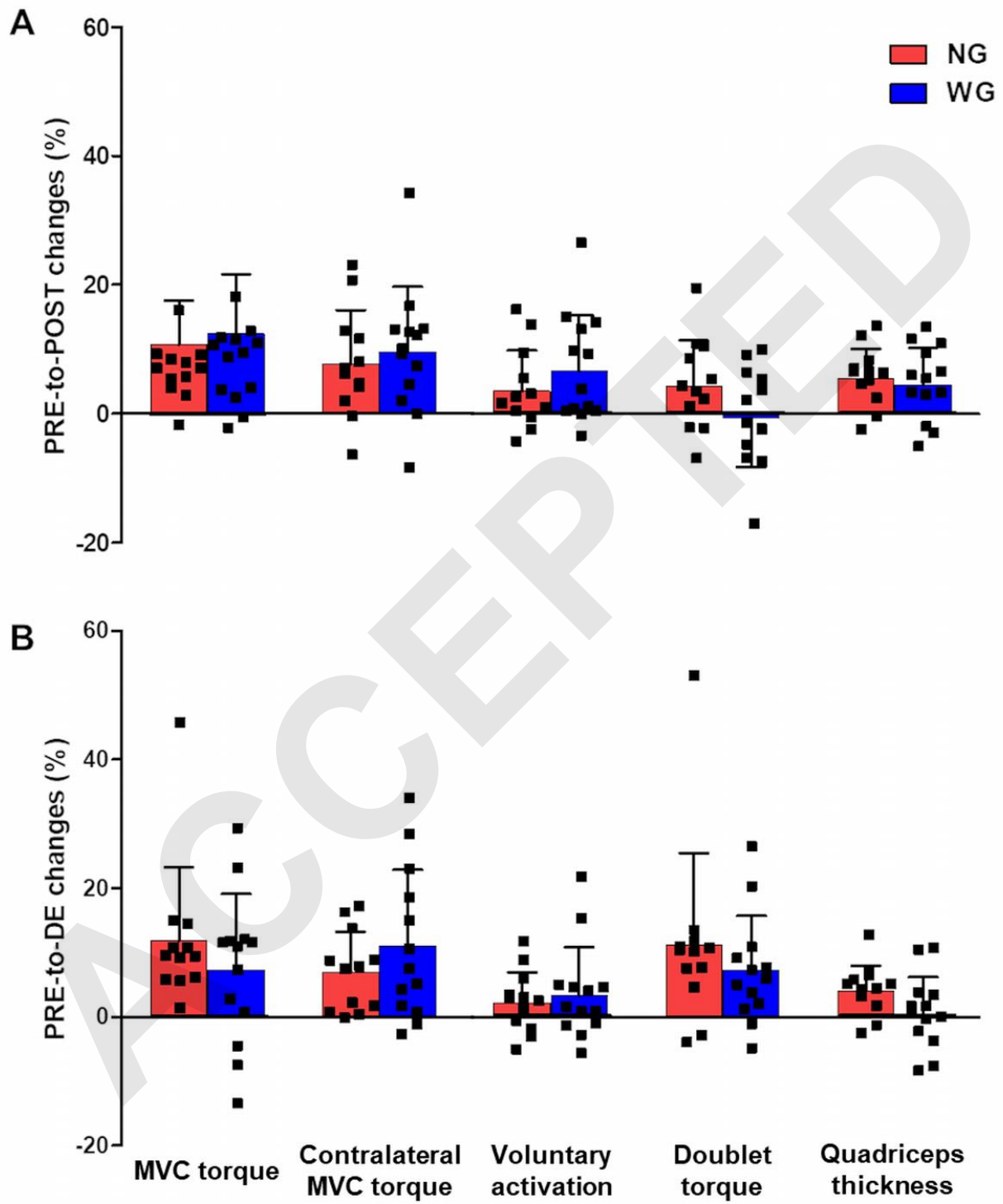


Figure 6

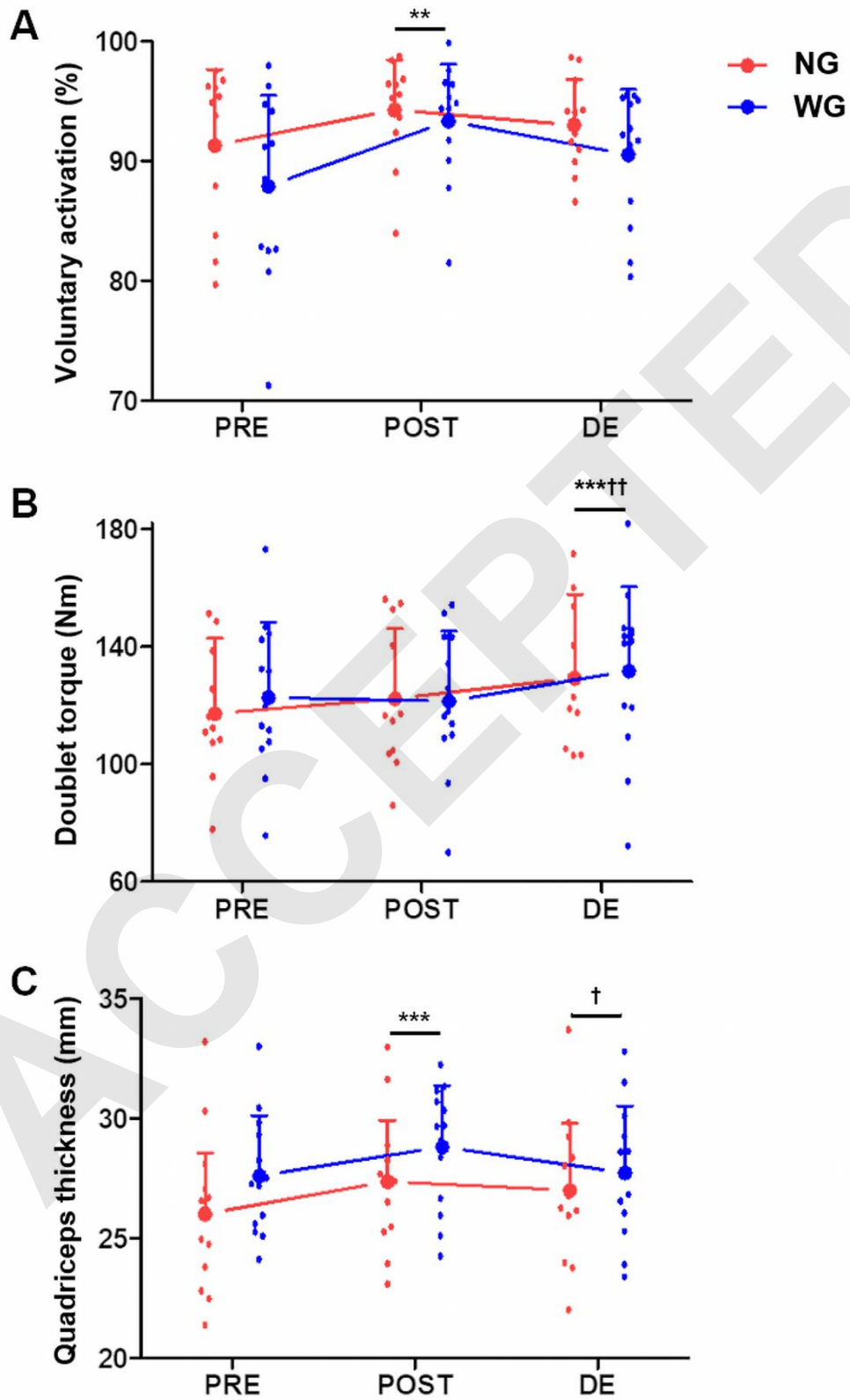


Figure 7

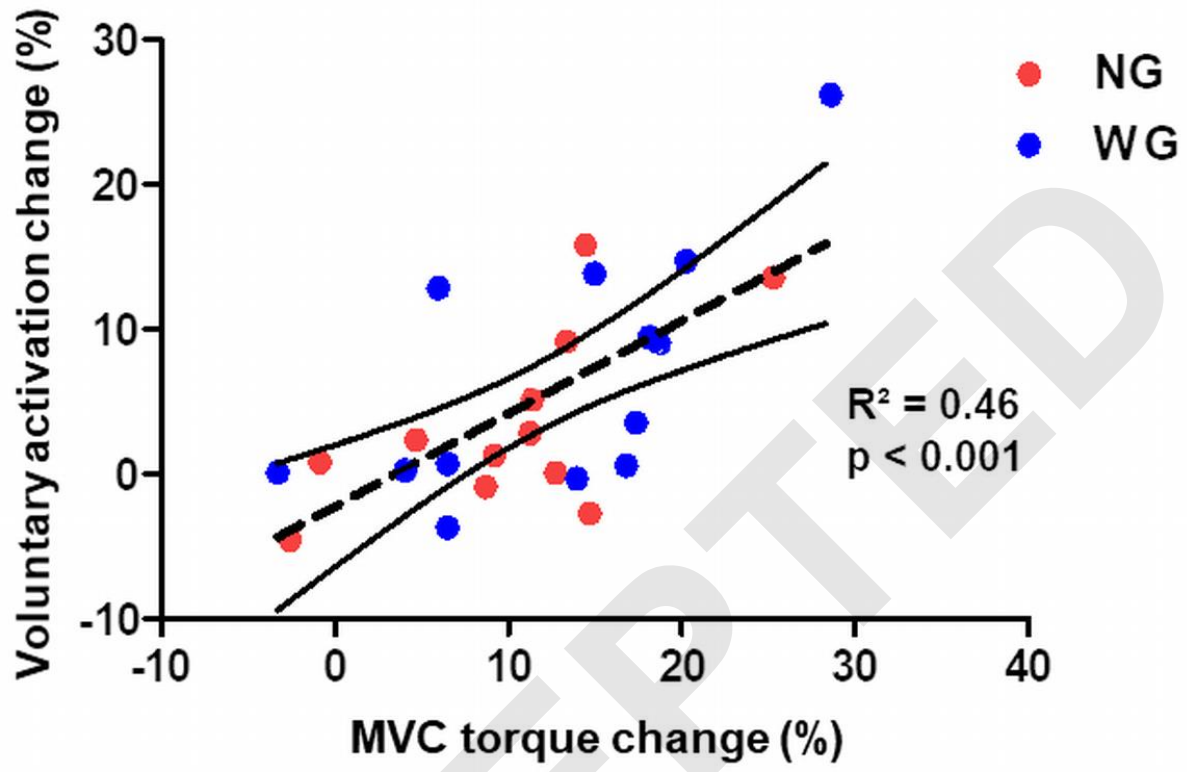


Table 1. Main characteristics of the participants by group.

	Control group (n = 11)	NG (n = 12)	WG (n = 13)
Age (year)	27 ± 9	31 ± 11	24 ± 6
Height (cm)	178 ± 7	178 ± 6	177 ± 5
Body mass (kg)	75 ± 8	70 ± 7	72 ± 9
Dominant leg (right/left)	9 / 2	9 / 3	11 / 2
Self-reported volume of physical activity (min/week)	322 ± 167	268 ± 146	298 ± 182

Data are mean ± SD. NG: narrow-pulse group; WG: wide-pulse group.

Supplemental Table S1. Neuromuscular variables for the control group (n = 11) at the beginning of the study (PRE), after 6 weeks (POST) and 12 weeks (DE) of usual activity.

	PRE	POST	DE	p-value
MVC torque (Nm)	313 ± 57	316 ± 51	315 ± 56	0.95
Voluntary activation (%)	90.5 ± 7.8	89.0 ± 7.0	88.8 ± 6.0	0.49
Contralateral MVC torque (Nm)	311 ± 57	314 ± 62	317 ± 60	0.75
MEP (% of maximal M-wave)	11.4 ± 7.1	11.1 ± 3.6	12.4 ± 4.0	0.82
Quadriceps muscle thickness (mm)	27.0 ± 3.4	27.3 ± 3.8	27.3 ± 3.8	0.57
Doublet torque (Nm)	120 ± 28	127 ± 33	127 ± 36	0.10

MVC, maximal voluntary contraction; MEP, motor evoked potential.

Supplemental Table S2. Muscle thickness of the four quadriceps heads for narrow-pulse and wide-pulse groups before (PRE) and after (POST) NMES training, as well as after detraining (DE).

	NG (n = 12)			WG (n = 13)		
	PRE	POST	DE	PRE	POST	DE
Vastus lateralis (mm)	26.5 ± 4.0	28.9 ± 4.4 ^{***}	27.9 ± 4.0 ^{***†††}	26.6 ± 2.1	28.4 ± 2.8 ^{***}	27.1 ± 2.8 ^{***†††}
Vastus medialis (mm)	31.6 ± 6.2	32.4 ± 4.7 [*]	33.6 ± 5.1 [*]	35.1 ± 6.4	37.0 ± 6.2 [*]	36.4 ± 6.7 [*]
Rectus femoris (mm)	24.8 ± 2.1	27.1 ± 2.7 ^{***}	25.6 ± 2.4 ^{*†††}	25.6 ± 2.1	27.2 ± 2.5 ^{***}	25.8 ± 2.1 ^{*†††}
Vastus intermedius (mm)	21.1 ± 4.8	21.0 ± 3.7	20.8 ± 3.8	23.2 ± 3.4	22.7 ± 3.6	21.7 ± 3.8

NG, narrow-pulse group; WG, wide-pulse group;. Significantly higher than PRE (***, p < 0.001; *, p < 0.05). Significantly lower than POST (†††, p < 0.001).