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ORIGINAL ARTICLE

Neuromuscular adaptations to wide-pulse high-frequency neuromuscular electrical stimulation training

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Abstract

Purpose No studies have evaluated the potential benefits of wide-pulse high-frequency (WPHF) neuromuscular electrical stimulation (NMES) despite it being an interesting alternative to conventional NMES. Hence, this study evaluated neuromuscular adaptations induced by 3 weeks of WPHF NMES.

Methods Ten young healthy individuals (training group) completed nine sessions of WPHF NMES training spread over 3 weeks, whereas seven individuals (control group) only performed the first and last sessions. Plantar flexor neuromuscular function (maximal voluntary contraction (MVC) force, voluntary activation level, H reflex, V wave, contractile properties) was evaluated before the first and last training sessions. Each training session consisted of ten 20-s WPHF NMES contractions (pulse duration: 1 ms, stimulation frequency: 100 Hz) interspaced by 40 s of recovery and delivered at an intensity set to initially evoke ~ 5% of MVC force. The averaged mean evoked forces produced during the ten WPHF NMES-evoked contractions of a given session as well as the sum of the ten contractions force time integral (total FTI) were computed.

Results Total FTI (+ 118 ± 98%) and averaged mean evoked forces (+ 96 ± 91%) increased following the 3-week intervention ($p < 0.05$); no changes were observed in the control group. The intervention did not induce any change ($p > 0.05$) in parameters used to characterize plantar flexor neuromuscular function.

Conclusion Three weeks of WPHF NMES increased electrically evoked forces but induced no other changes in plantar flexor neuromuscular properties. Before introducing WPHF NMES clinically, optimal training program characteristics (such as frequency, duration and intensity) remain to be identified.

Keywords Extra-force · H reflex · V wave · Maximal voluntary contraction · Maximal voluntary activation level · Contractile properties

Abbreviations

AQAP	Physical activity auto-questionnaire
EMG	Electromyography
EMG_{max}	Maximal electromyography activity recorded during a maximal voluntary contraction
FTI	Force time integral
H_{max}	Maximal H-reflex amplitude
I_{Hmax}	Stimulation intensity required to evoke the maximal *soleus* H-reflex amplitude
I_{Mmax}	Stimulation intensity required to evoke maximal *M*-wave amplitude
I_{WPHF}	Stimulation intensity necessary to evoke a force corresponding to 5% of MVC force
M_{max}	Maximal *M*-wave amplitude
M_{sup}	Superimposed *M*-wave peak-to-peak amplitude
MVC	Maximal voluntary contraction
NMES	Neuromuscular electrical stimulation

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PS10	Supramaximal 10-Hz paired stimulation
PS100	Supramaximal 100-Hz paired stimulation
RMS_{max}	Maximal root mean square
SS	Single stimulation
V/M_{sup}	Ratio between *V*-wave and superimposed *M*-wave peak-to-peak amplitudes
VAL	Voluntary activation level
WPHF	Wide-pulse high frequency

Introduction

Neuromuscular electrical stimulation (NMES, i.e., transcutaneous intermittent tetanic stimuli triggering muscle contractions), a widely used paradigm to improve skeletal muscle function in rehabilitation and training programs (Maffiuletti 2010), presents inherent limitations. First, substantial discomfort (Delitto et al. 1992) results from the need to deliver NMES at maximal tolerable intensity (as strength gains primarily depend on the force level evoked by NMES (i.e., training intensity) (Snyder-Mackler et al. 1994)), preventing the implementation of effective NMES programs in certain frail populations. Second, repeated NMES contractions lead to a rapid and large reduction in the evoked force ("exaggerated fatigue") caused by the non-physiological (spatially fixed and synchronous) motor unit recruitment (Bickel et al. 2011; Gregory and Bickel 2005) as compared to voluntary contractions (Theurel et al. 2007).

Recently, a new NMES modality was proposed to circumvent some of these limitations. This NMES modality—named wide-pulse high-frequency NMES (or WPHF NMES)—is characterized by high stimulation frequencies (> 80 Hz) and long pulse durations (1 ms) compared to conventional NMES current characteristics (frequency range: 15–80 Hz; pulse duration range: 0.1–0.5 ms) (Vanderthommen and Duchateau 2007; Collins 2007). It results in preferential depolarization of large sensory diameter afferents (mainly Ia afferents) over motoneurons as the former present lower rheobase and longer strength–duration time constants (Kiernan et al. 2004; Veale et al. 1973). Once depolarized, these afferents may reflexively recruit motoneurons at the spinal cord following the size principle (Collins 2007; Collins et al. 2001, 2002). For this reflexive motor unit recruitment to participate in force production, antidromic block should be minimized and, therefore, low current intensity (inducing ~ 5–10% maximal voluntary contraction (MVC) force) is a pre-requisite (Dean et al. 2007; Bergquist et al. 2011). If such a pre-requisite would inherently compromise the training benefits associated with classical NMES, a gradual increase in force ('extra force', up to 70% MVC force) is observed in some (the so-called 'responders'), but not all (i.e., 'non-responders') individuals over the course of WPHF NMES-evoked contractions despite constant stimulation intensity (Collins et al. 2001, 2002; Neyroud et al. 2014, 2016, 2018; Wegrzyk et al. 2015). Nevertheless, it is unknown whether individual responder status evolves with repetitive exposure to WPHF NMES. It can be anticipated that, when extra force develops, chronic exposure to WPHF NMES might result in a stimulus sufficient to increase muscle strength. Further, multiple WPHF NMES sessions might strengthen the I_a afferents—α-motoneuron connections by repetitively stimulating the reflexive motor unit recruitment pathway, leading to greater extra forces development towards the end of the training period irrespective of the initial responder status (i.e., potentially resulting in non-responders becoming responders).

Despite being a promising training paradigm, to date no study has assessed the chronic adaptations induced by repeated sessions of WPHF NMES. Previous studies found that 3–6 weeks of *classical* NMES (i.e., depolarization of axonal terminals mainly) resulted in strength gains that could be ascribed to neural adaptations (Gondin et al. 2006a; Maffiuletti et al. 2002, 2003). Based on this knowledge and the compelling evidences (mainly from nerve blockade experiments) suggesting that WPHF NMES-evoked force can be partly ascribed to a reflexive motor unit recruitment [see (Collins 2007; Bergquist et al. 2011) for review], it can be expected that WPHF NMES would also result in spinal and/or supraspinal adaptations, even at relatively low force levels. The present study thus aimed at evaluating the effects of a 3-week WPHF NMES training protocol on plantar flexor neuromuscular function. It was hypothesized that WPHF NMES training would (1) induce neural adaptations resulting in enhanced MVC force and (2) result in greater extra forces over the course of the training, potentially changing individual responder status.

Methods

Subjects

Seventeen healthy participants (7 women, 10 men; 25 ± 3 years; 67 ± 10 kg; 172 ± 10 cm) volunteered to take part in this study. All participants were physically active [average physical activity score of 9.8 ± 0.6, corresponding to a satisfactory level of physical activity according to the physical activity auto-questionnaire (AQAP) (Vol et al. 2011)] but none of them were enrolled in any other supervised strength and/or endurance training program. Further, participants were asked not to engage in any non-habitual physical activity during the whole duration of the study. Participants were split into a control group (3 women, 4 men) and a training group (4 women, 6 men) that were similar in terms of age (25 ± 5 years vs. 24 ± 1 years for the control and training group,

respectively), weight (62 ± 10 kg vs. 70 ± 16 kg), height (169 ± 8 cm vs. 174 ± 10 cm) and physical activity score (9.8 ± 0.8 vs. 9.9 ± 0.5).

The study protocol was approved by the Ethics Committee of the Vaud canton (protocol 2016-00767) and was in accordance with the latest update of the Helsinki Declaration. Informed consent was obtained from all individual participants included in the study.

Experimental protocol

The training program consisted of nine sessions spread over a 3-week period with the first and last training sessions (hereafter referred to as sessions 1 and 9) comprising, in addition to the training protocol, an evaluation of the neuromuscular function of the plantar flexors.

All participants were familiarized with the different procedures before session 1. Participants in the training group completed all the training sessions, whereas participants in the control group only took part in sessions 1 and 9 for evaluation purpose. Training and testing procedures were conducted on the dominant leg (determined as the leg used to kick a ball) with knee and ankle angles set to 90°. An overview of the experimental protocol is depicted in Fig. 1.

Training protocol

During each of the nine training sessions, electrical pulses with a duration of 1 ms were delivered by a high-voltage (maximal voltage 400 V) constant-current stimulator (modified model DS7AH, Digitimer, Hertfordshire, UK). NMES was applied to the *triceps surae* muscle belly via two 10 × 5-cm electrodes (VS10050, Verity Medical, NeuroTrac, Braishfield, UK) positioned over the *gastrocnemii* (~ 5 cm below the popliteal fossa) and *soleus* (~ 10 cm above the calcaneus) muscles (Neyroud et al. 2014). The stimulation intensity necessary to evoke a force corresponding to 5% of MVC force (I_{WPHF}) was determined by delivering 1-s long 100-Hz trains. This evoked-force level was chosen to limit antidromic block. Subsequently, ten 20-s WPHF NMES contractions were evoked at this intensity. This rather long contraction duration was chosen to enable time for extra-force development (Dean et al. 2007). As WPHF-evoked contractions were longer than classical NMES contractions, a lower number of contractions were considered to achieve a comparable stimulation duration per session as classically employed [i.e., 200 s in the present study vs. 160–180 s in (Gondin et al. 2006b, c; Jubeau et al. 2006; Maffiuletti et al. 2003)]. Each contraction was separated from the previous one by 40 s, i.e., duty cycle was 33% (Neyroud et al. 2014). Participants were asked to remain relaxed during the entire WPHF NMES protocol. Occasionally, when force did not

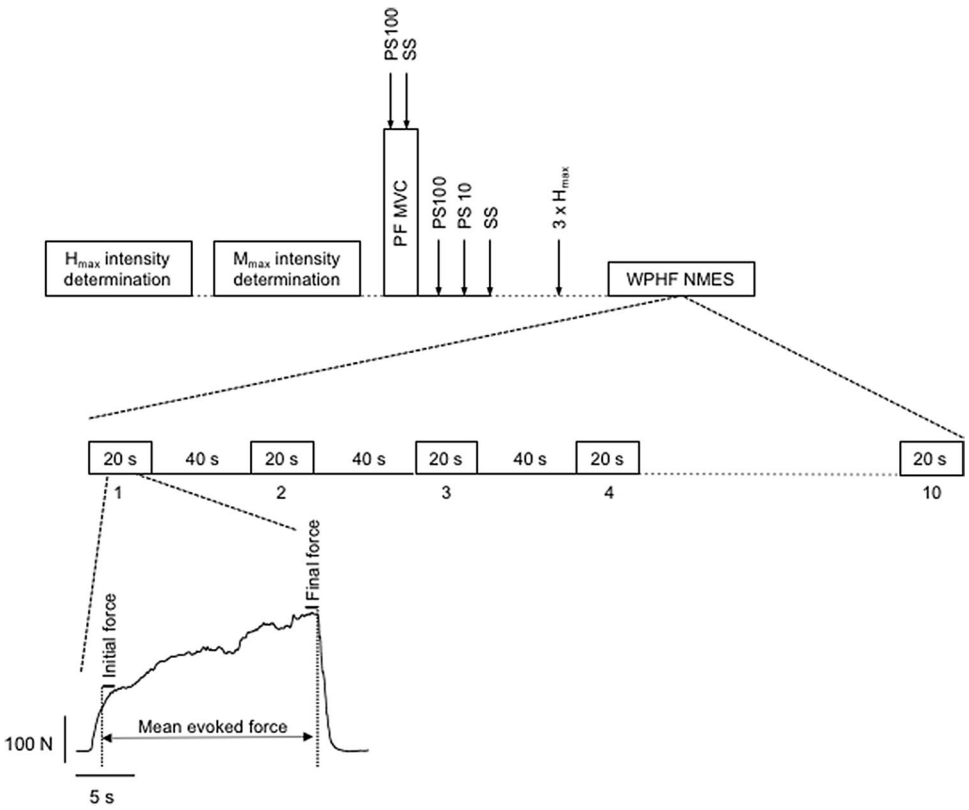

Fig. 1 Schematic representation of the experimental protocol. The whole protocol was performed during the first and last sessions, whereas only the 'WPHF NMES' part was done during training sessions 2–8. *MVC* maximal voluntary contraction, H_{max} maximal H-reflex, M_{max} maximal *M*-wave, *PF* plantar flexor, *PS100* 100-Hz paired stimulation, *PS10* 10-Hz paired stimulation, *SS* single stimulation, *WPHF NMES* wide-pulse high-frequency neuromuscular electrical stimulation. Solid horizontal bars on the top of the typical WPHF NMES contraction highlight the time windows over which the initial and final forces were measured, whereas the vertical dashed lines show the point between which mean force was measured

return to baseline level in between evoked WPHF NMES contractions, the investigators asked the participant to ensure his/her stimulated muscle was fully relaxed.

During sessions 4 and 7, plantar flexor MVC force was re-evaluated to monitor potential changes in MVC force, in which case the 5% MVC target force was re-calculated. Stimulation intensity was readjusted at the beginning of each session.

Neuromuscular function evaluation

During the first experimental session, optimal position of the surface electromyography (EMG) and stimulating electrodes was determined and marked on the skin with indelible ink for subsequent repositioning. A circular cathode (1-cm diameter, Kendall Meditrace 100, Tyco, Cork, Ireland) was positioned in the popliteal fossa and a rectangular anode (5 × 10 cm, VS10050, Verity Medical, NeuroTrac, Braishfield, UK) was placed on the anterior surface of the knee. Single and paired stimuli at different intensities were delivered by a high-voltage (maximal voltage 400 V) constant-current stimulator (modified model DS7AH, Digitimer, Hertfordshire, UK) with pulse duration set to 1 ms. Stimulation intensities required to evoke the largest *soleus H*-reflex (H_{max}) and *M*-wave (M_{max}) amplitude responses were determined on sessions 1 and 9. H_{max} was first roughly determined by increasing the stimulation intensity by increments of 5 mA with stimuli delivered every 8 s. Subsequently, the intensity required to evoke H_{max} (I_{Hmax}) was refined by delivering three single stimuli at each intensity (2-mA steps over a 20-mA range and separated by 8 s), over the 20-mA range centered on the pre-defined I_{Hmax} (Neyroud et al. 2018). The intensity required to evoke M_{max} (I_{Mmax}) was then determined. We considered I_{Mmax} to be reached when a subsequent additional increase of 20% (i.e., supramaximal stimulation intensity) did not result in any increases in either *M*-wave amplitude or peak twitch force. Thereafter, participants warmed up by performing 8 to 10 plantar-flexions at 20–80% of their self-estimated MVC force. Then, three to five 4–5 s plantar-flexion MVCs were performed, with rest periods of 30–60 s in between. Participants were asked to develop the strongest force they could within 1–2 s and to hold this force for about 3 s. The two best MVC forces had to be within 5% of each other. Apart from the first MVC that did not include any electrical stimulations, one supramaximal 100-Hz paired stimulation (superimposed PS100) and one single supramaximal stimulation (superimposed single stimulation), separated by 1–2 s, were delivered during all subsequent MVCs to evaluate voluntary activation level and V wave, respectively. In addition, one PS100, one supramaximal 10-Hz paired stimulation (PS10) and one single supramaximal stimulation were delivered 2 s after the force signal returned to baseline (i.e., potentiated stimulations), with 2 s of rest between each stimulation. After 60 s of rest, 3 single stimuli were delivered at I_{Hmax}, with an interval of 8 s in between.

Data collection and analysis

Force

A custom built isometric ergometer equipped with a pedal coupled to a strain gauge (capacity: 110 N m, Vishay Micro Measure, Raleigh, USA) was used to record voluntary and evoked plantar flexion forces. Participants were seated on a vertically adjustable stool and asked to keep their arms relaxed either on the sides of the body or crossed over the chest. Hip, knee and ankle angles were set to 90°. To limit the contribution of muscle groups other than plantar flexors, the thigh was clamped down with a velcro strap proximal to the knee. The foot was strapped to the pedal at the ankle and metatarsi levels. An analog-to-digital conversion system (MP150, BIOPAC, Goleta, USA) was used to acquire the force signals at 1.25 kHz.

MVC force was considered as the peak force developed during an MVC. At time points where several MVCs were performed (i.e., at the beginning of the sessions), the highest MVC force was considered for further analysis. The amplitudes of the superimposed and potentiated evoked forces associated with this highest MVC were measured. PS100, PS10 and peak twitch force were quantified to evaluate muscle contractility.

Voluntary activation level (VAL) was quantified as follows: (1 − (superimposed PS100 × (force level at stimulation/MVC force)/potentiated PS100)) × 100 (Strojnik and Komi 1998).

For each of the WPHF-evoked contraction, the force time integral (FTI) was quantified (Neyroud et al. 2014). The sum of the ten contractions FTI was then calculated to determine the total FTI for a given session. In addition, the mean force evoked between the 2nd and last second of each contraction was calculated (referred to as mean evoked force, see Fig. 1). The mean forces produced during the 2nd second (referred to as initial evoked force) as well as during the last second (referred as final evoked force) of each contraction were also extracted (see Fig. 2a, b) (Neyroud et al. 2016). The respective average of these initial, final and mean evoked forces produced during the 10 evoked contractions of each session were computed. Individuals showing final evoked forces greater than 5% MVC were considered as responders, whereas the others were classified as non-responders.

EMG

Soleus, gastrocnemius lateralis and *gastrocnemius medialis* EMG activity was recorded using pairs of circular (1-cm

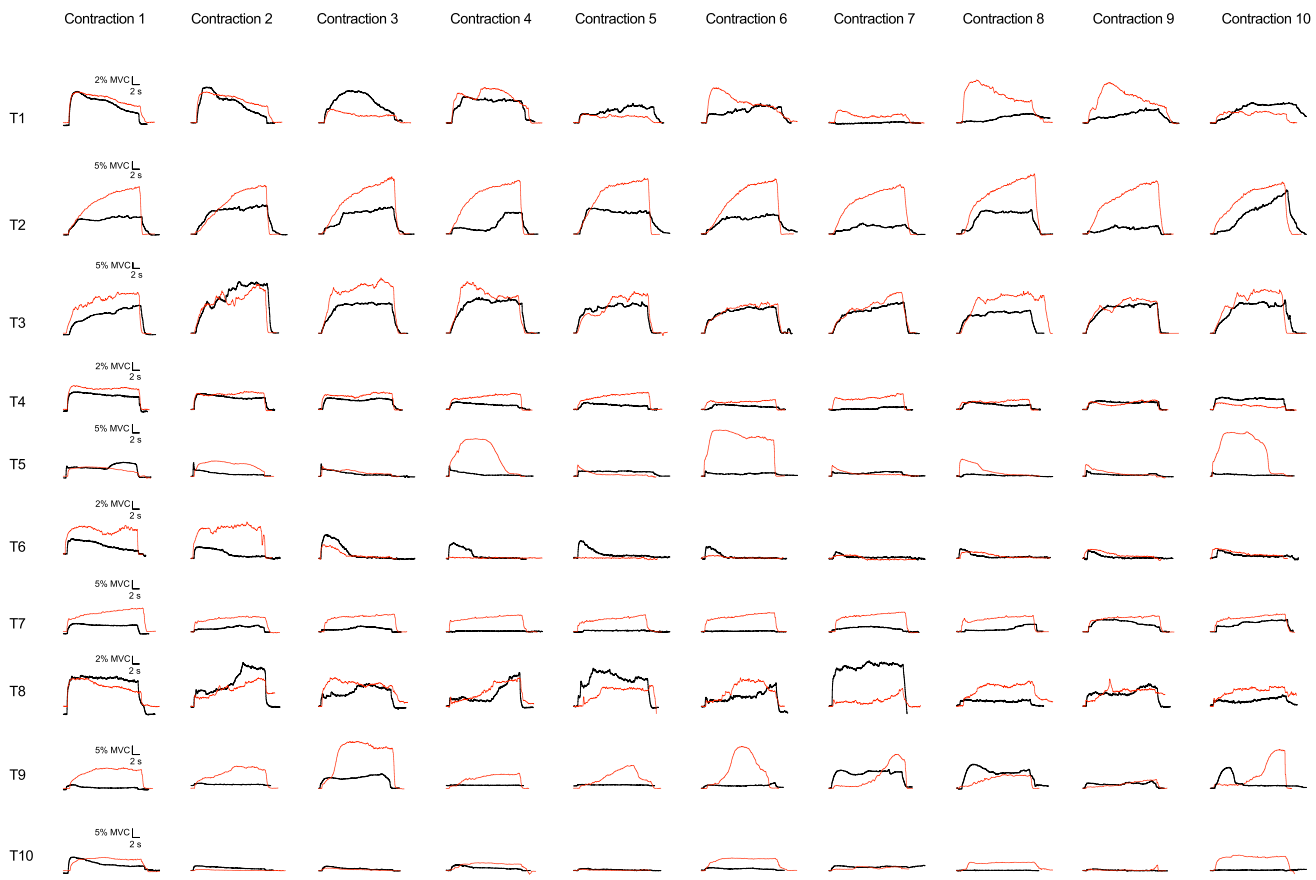

Fig. 2 Original traces of the ten WPHF NMES-evoked contractions recorded during the first (black) and last (red) training session for all trained participants. T1–10 indicate participant identities

recording diameter) silver chloride (Ag/AgCl) surface electrodes (Kendall Meditrace 100, Tyco, Cork, Ireland) positioned lengthwise over the muscle belly with an inter-electrode distance (center-to-center) of 2 cm (Hermens et al. 2000). The reference electrode was placed over the ipsilateral patella. The skin was shaved and cleaned with alcohol to obtain low inter-electrode resistance. EMG signals were amplified with a gain of 1000, digitized at a sampling frequency of 5 kHz, filtered with a bandwidth frequency between 10 and 500 Hz and recorded by an analog-to-digital conversion system (MP150, BIOPAC Systems, Goleta, USA). EMG as well as force signals were stored and analyzed offline with commercial software (Acqknowledge, BIOPAC Systems, Goleta, USA).

M_{max} was measured as the peak-to-peak amplitude from the single supramaximal stimulation delivered at rest and used to monitor changes in neuromuscular propagation. For H_{max}, the average peak-to-peak amplitude of the three responses recorded at each time point was considered and normalized by M_{max} (H_{max}/M_{max} ratio) to evaluate the balance between excitation and inhibition at the spinal cord. *V*-wave peak-to-peak amplitude was measured from the single supramaximal stimulation delivered during MVC and normalized by the amplitude of the *M*-wave associated with the same stimulus (V/M_{sup} ratio) to assess spinal/supraspinal changes (Aagaard et al. 2002). Maximal EMG activity was measured over a 500-ms time window centered on MVC force using the root mean square (RMS_{max}) of the raw signal. To account for potential peripheral contamination, RMS_{max} was normalized by M_{max} (RMS_{max}/M_{max}) and used as an additional index of muscle activation. For all WPHF NMES-evoked contractions, sustained EMG activity (i.e., the EMG activity that persisted after stimulation termination) was measured immediately after the last pulse of the WPHF trains, over a 500-ms time window, as the RMS of the raw EMG signal. The average sustained EMG activity recorded during each contraction of a given session was computed and normalized by the RMS_{max} (Neyroud et al. 2018).

Statistical analysis

Two-way ANOVAs (group × session), with session as a repeated measure, were conducted for all dependent

variables. When significant differences were identified by the ANOVA, follow-up Sidak post hoc analyses were performed. The alpha level for statistical significance was set to $p < 0.05$. All analyses were conducted using Prism (version 7.0b, GraphPad, La Jolla, USA). Data are reported as mean ± SD.

Results

WPHF evoked contractions

Original traces showing WPHF-evoked contractions are depicted in Figs. 2 and 3 for trained and control participants, respectively. The intensity of stimulation required to evoke ~ 5% of MVC force did not differ between groups ($p = 0.605$) or between sessions 1 and 9 ($p = 0.117$; Table 1). This intensity of stimulation elicited an initial force recorded during the first contraction of the first session of 6.6 ± 2.4% and 6.9 ± 1.6% of MVC for the training and control groups, respectively ($p = 0.760$). Further, the averaged initial WPHF-evoked force was not significantly different between the groups ($p = 0.494$) or between sessions 1 and 9 ($p = 0.425$, Fig. 4a). Higher averaged final and mean evoked forces were observed during session 9 in the training group (group x session interaction, $p = 0.042$ and $p = 0.039$ for final and mean evoked forces, respectively, Fig. 4b, c). Similarly, an increased total FTI was observed in the training group for session 9 (group × session interaction, $p = 0.020$, Fig. 3d). *Soleus* sustained EMG activity did not differ between groups ($p = 0.709$) and sustained EMG activity changes over time were not significant (+ 2.8 ± 5.0% RMS_{max} in the training group and − 0.3 ± 1.6% RMS_{max} in the control group; $p = 0.216$, Fig. 4e; Table 1). Similar findings were found for *gastrocnemius lateralis* and *gastrocnemius medialis* muscles (Table 2).

Based on the final evoked force, three control (C3, C6 and C7) and three 'trained' (T2, T3 and T8) participants could be classified as responders (represented with filled triangles in Fig. 4b) for session 1. If none of the participants in the control group showed a shift in their responder status between sessions 1 and 9, two additional 'trained' participants (T7 and T9) could be classified as responders in session 9. Also, one of the 'trained' participants (T8) was classified as a responder in session 1 (i.e., showing a final evoked force slightly greater than 5% MVC) but not anymore in session 9 (i.e., final evoked force was slightly lower than 5% MVC). The two participants who became responders in session 9 showed an increased sustained EMG activity compared to session 1 (T7 and T9 (filled circles) in Fig. 4e). Noteworthy, some of the participants who were initially classified as non-responders showed increases in total FTI, averaged mean and final forces over the course of the training program (Fig. 5).

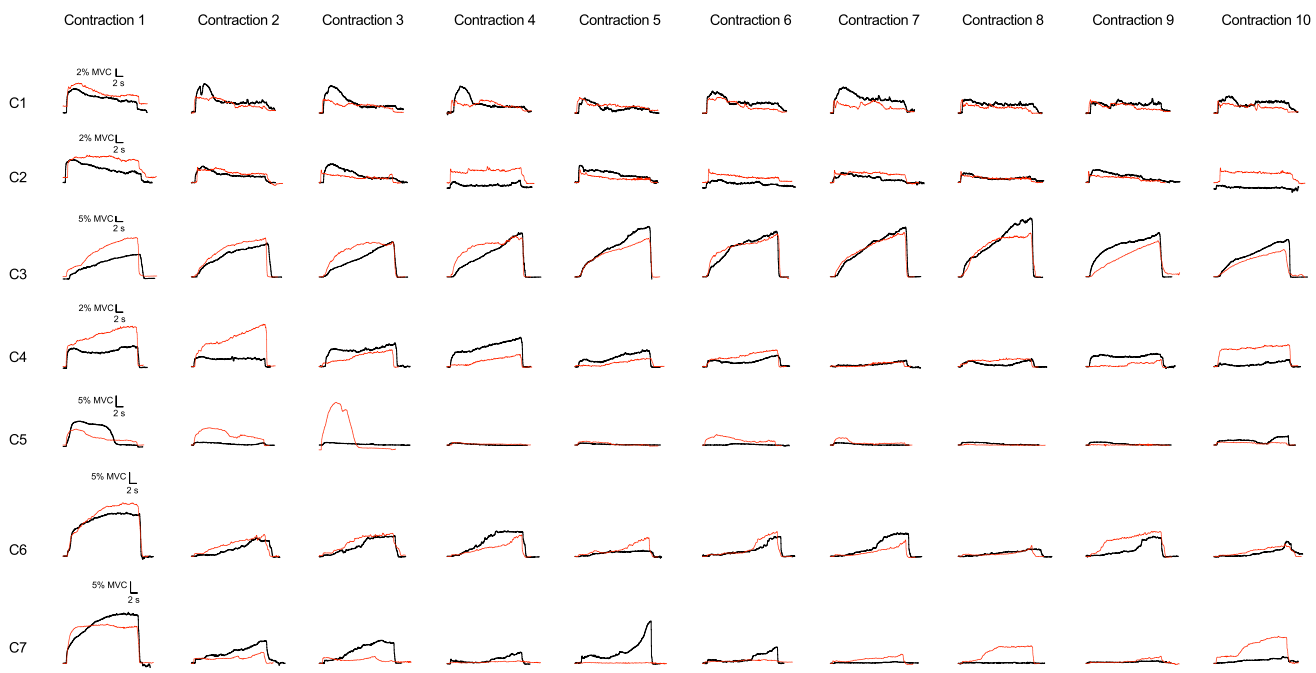

Fig. 3 Original traces of the ten WPHF NMES-evoked contractions recorded during the first and last training sessions for all control participants. C1–7 indicate participant identities

Table 1 Stimulation intensity and neuromuscular parameters recorded during the first and last sessions

	Control group		Training group	
	Session 1	Session 9	Session 1	Session 9
EMG parameters				
I_{Hmax}, mA	50.4 ± 20.2	40.6 ± 18.8	55.8 ± 15.9	54.3 ± 16.6
I_{Mmax}, mA	159.0 ± 35.7	178.7 ± 44.9	200.8 ± 57.5	209.4 ± 51.7
I_{WPHF}, mA	11.4 ± 3.2	10.5 ± 2.5	13.4 ± 9.1	10.0 ± 3.3
Soleus V/M_{sup}, %	22 ± 14	28 ± 17	27 ± 23	31 ± 26
Soleus H_{max}/M_{max}, %	46 ± 23	40 ± 24	42 ± 20	43 ± 23
Soleus M_{max}, mV	10.3 ± 4.0	11.2 ± 3.2	10.3 ± 2.3	11.3 ± 2.4
Force parameters				
MVC, *N*	829 ± 168	858 ± 259	904 ± 243	880 ± 301
VAL, %	89 ± 10	89 ± 10	85 ± 11	88 ± 15
PS100 force, *N*	314 ± 48	311 ± 38	325 ± 118	302 ± 73
PS10 force, *N*	306 ± 46	298 ± 38	289 ± 104	293 ± 81
Peak twitch force, *N*	204 ± 33	202 ± 29	210 ± 64	198 ± 47

$N = 7$ in the control group and 10 in the training group except for I WPHF, for which $N = 8$, as the stimulation intensity used during the first session of one participant and the last session of another one was not recorded. I_{Hmax} intensity of stimulation to elicit maximal *H* reflex, I_{Mmax} intensity of stimulation to elicit maximal *M* wave, I_{WPHF} intensity to elicit 5% of maximal voluntary contraction (MVC) force with a 1-s WPHF NMES train, RMS_{max}/M_{max} root mean square of the maximal electromyographic activity normalized to the peak-to-peak *M*-wave amplitude (M_{max}), H_{max}/M_{max} maximal *H*-reflex normalized to M_{max}, V/M_{sup} *V*-wave amplitude normalized to the amplitude of the superimposed *M*-wave associated with the same stimulus, *MVC* maximal voluntary contraction, *VAL* voluntary activation level, *PS100* 100-Hz paired stimulation, *PS10* 10-Hz paired stimulation

Neuromuscular function

Typical traces for neuromuscular function variables are depicted in Fig. 6. MVC and evoked forces were not different between groups nor were they affected by training ($p \geq 0.328$, Table 1). Similarly, no group or training-induced differences were found for any of the other neuromuscular parameters [i.e., M_{max}, H_{max}/M_{max}, VAL, RMS_{max}/M_{max} or V/M_{sup} ($p \geq 0.100$, Tables 1, 2)].

Discussion

The present study evaluated for the first time the effects of chronic exposure to WPHF NMES on plantar flexor neuromuscular function. In contrast with our hypotheses, 3 weeks (9 sessions) of WPHF NMES did not induce neural adaptations and hence did not increase MVC force. Yet, as expected, WPHF NMES training resulted in higher mean-evoked forces and total FTI during the last training session compared to the first one. Further, some individuals who were classified as non-responders during the first WPHF NMES session became responders over the course of the training program, whereas no such status changes were observed in the control group.

Lack of MVC force increase and neural adaptations

Previous studies showed that 3–5 weeks of classical NMES training (with evoked forces ranging from 50 to 80% MVC) (Gondin et al. 2006a, b; Jubeau et al. 2006; Maffiuletti et al. 2002; Pichon et al. 1995) induced gains in MVC forces (~ 20%) that could be attributed to increased neural drive as evidenced by increases in VAL, RMS_{max}/M_{max} and V/M_{sup} alongside with an unchanged H_{max}/M_{max} ratio (Gondin et al. 2006a, b; Jubeau et al. 2006; Maffiuletti et al. 2002). In contrast to these previous studies using classical NMES paradigms, our findings revealed no neural adaptations (i.e., no changes in VAL, RMS_{max}/M_{max} or V/M_{sup}) following 3 weeks of WPHF NMES. It, therefore, appears that, despite the fact that WPHF NMES potentially results in contractions involving central pathways to a greater extent than classical NMES, the contractile stress imposed by the WPHF NMES protocol was not sufficient to trigger neuromuscular adaptations. Indeed, the reasoning behind the idea that WPHF NMES might potentially represent a more efficient alternative to classical NMES is the associated extra-force production. For extra-force production to be possible, stimulation intensity should be kept relatively low such that antidromic collision is prevented; as a result, participants not showing extra forces will only experience minimal muscle tension and thence minimal contractile

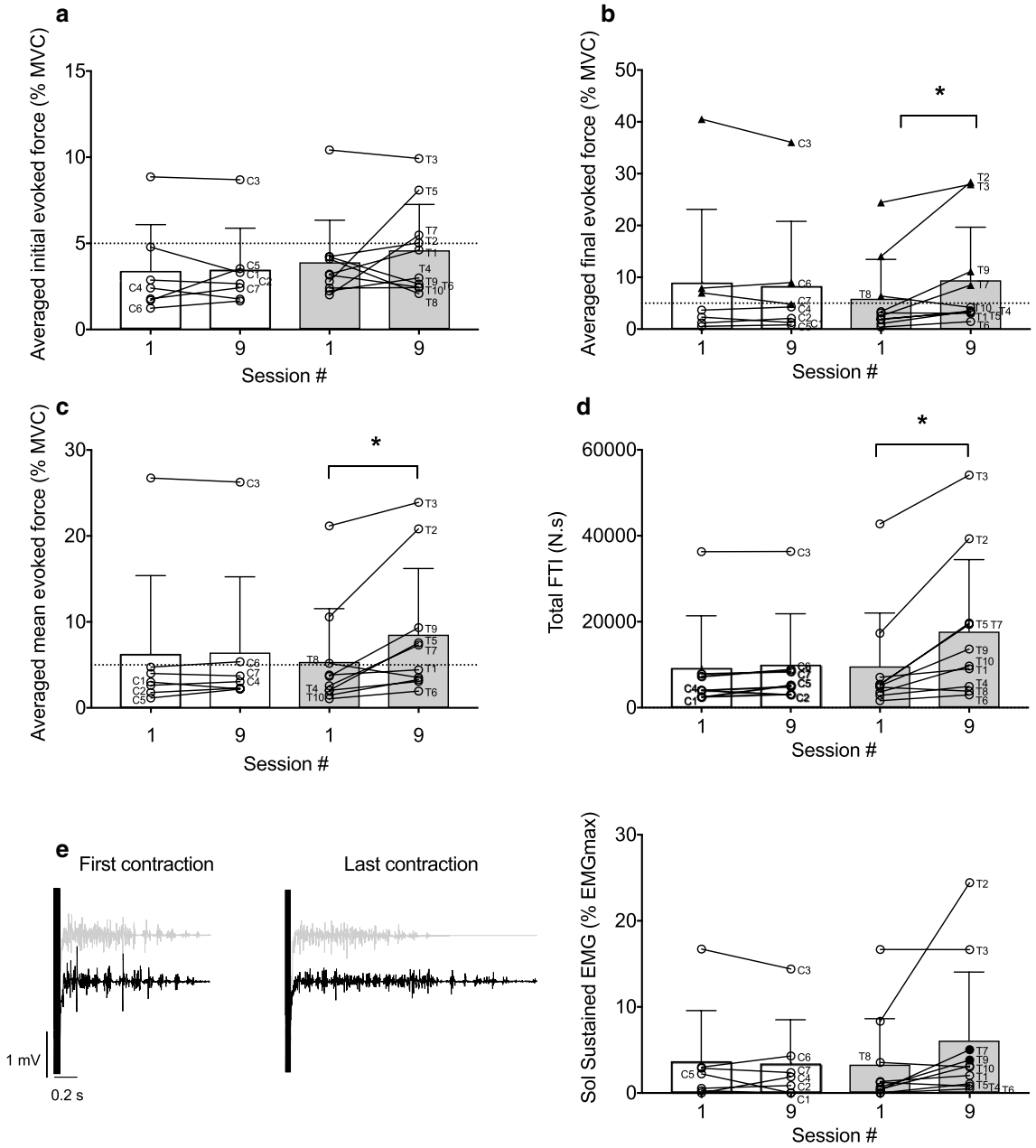

Fig. 4 WPHF NMES parameters recorded during the first (#1) and last (#9) training session. **a**–**d** Averaged initial (**a**), final (**b**) and mean (**c**) evoked forces and total force time integral (FTI, **d**). **e** Typical traces of *soleus* (Sol) sustained electromyography (EMG) activity recorded during the first (black) and last (grey) training sessions as well as averaged Sol sustained EMG activity for the control (clear bars) and training (filled bars) group. In panels B, participants considered as responders are represented by filled triangles. The horizontal dashed line shown on panels a–c indicates the initial targeted force (i.e., 5% MVC force). *Significant difference ($p < 0.05$), $N = 7$ for the control group and 10 for the training group. T1–10 and C1–7, respectively, indicate trained and control participant identities

stress. Ergo, the low number of individuals being responders during session 1 might partly explain the overall absence of MVC force improvement. Indeed only 30% (i.e., 3/10 in the training group) of the participants were classified as responders during the first session—representing a relatively low proportion of responders and contrasting with a previous study reporting extra force occurrence in around 60% of individuals (Wegrzyk et al. 2015). Further, none of the participants taking part in the training protocol reached more than 30% of their MVC force, while we recently observed that WPHF NMES-evoked forces may reach up to 70% MVC with similar stimulation conditions (Neyroud et al. 2018). Thus, similarly to classical NMES, strength gains induced by WPHF NMES training appear also to be proportional

Table 2 *Gastrocnemius lateralis* (GL) and *gastrocnemius medialis* (GM) electromyographic parameters recorded during the first and last sessions

	Control group		Training group	
	Session 1	Session 9	Session 1	Session 9
GL RMS_{max}/M_{max}, %	4.5 ± 2.7	4.4 ± 2.2	4.4 ± 1.7	4.5 ± 1.5
GM RMS_{max}/M_{max}, %	4.6 ± 1.0	4.7 ± 2.0	4.4 ± 1.4	4.4 ± 1.5
GL V/M_{sup}, %	15 ± 10	19 ± 16	19 ± 15	24 ± 17
GM V/M_{sup}, %	20 ± 11	31 ± 36	22 ± 16	26 ± 20
GL H_{max}/M_{max}, %	20 ± 28	14 ± 20	13 ± 15	8 ± 10
GM H_{max}/M_{max}, %	21 ± 8	21 ± 14	34 ± 34	23 ± 17
GL M_{max}, mV	7.6 ± 5.8	5.5 ± 1.9	7.4 ± 3.9	6.0 ± 1.9
GM M_{max}, mV	6.6 ± 3.6	7.4 ± 2.0	6.8 ± 4.0	6.6 ± 2.5
GL sustained EMG, % EMG_{max}	0.9 ± 1.7	0.6 ± 1.3	2.6 ± 5.3	3.0 ± 4.7
GM sustained EMG, % EMG_{max}	1.5 ± 2.4	1.9 ± 4.2	2.9 ± 6.6	2.8 ± 3.9

$N = 7$ for the control group and $N = 10$ for the training group. RMS_{max}/M_{max} root mean square of the maximal electromyographic activity normalized to the maximal M-wave amplitude (M_{max}), H_{max}/M_{max} maximal H-reflex amplitude normalized to M_{max}, V/M_{sup} V-wave amplitude normalized to the amplitude of the superimposed M-wave associated with the same stimulus, EMG_{max} maximal electromyography activity recorded during a maximal voluntary contraction

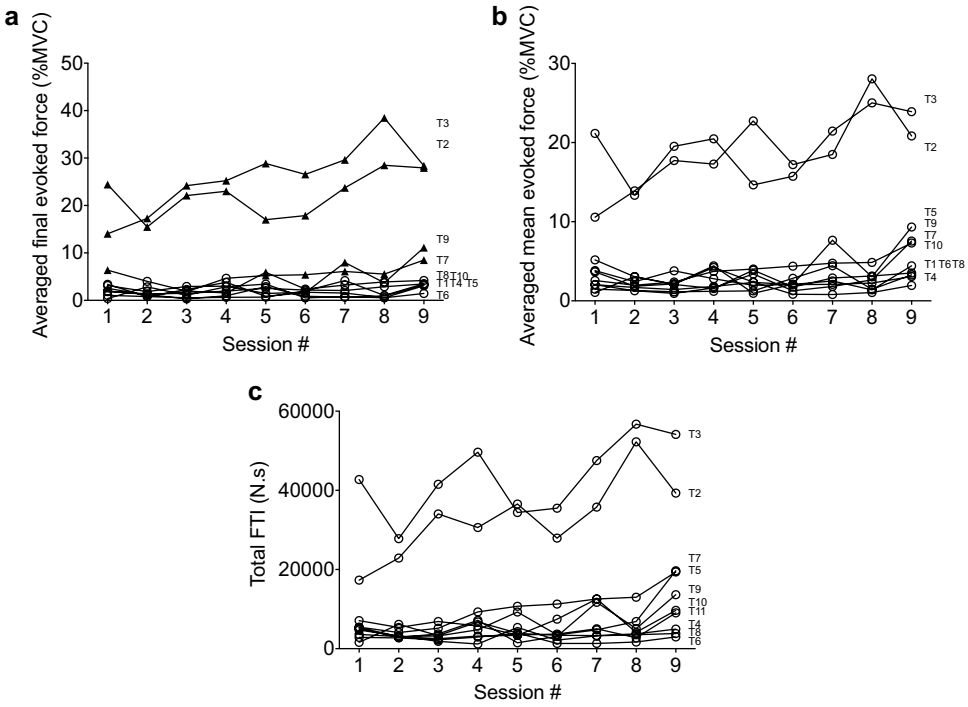

Fig. 5 WPHF NMES parameters recorded during the nine training sessions for the training group. Panels a–c show averaged final (**a**), mean (**b**) and total force time integral (FTI, **c**). In **a**, for each session, participants considered as responders are represented by filled triangles. T1–10 indicate participant identities

to the level of force developed (i.e., training intensity) [see (Maffiuletti 2010) for review]. It cannot be excluded that MVC force gains could have occurred with a similar WPHF training program entailing greater extra forces (e.g., > 20–30% MVC).

Modulation of WPHF-evoked force

The potential benefits of extra-force production for training and/or rehabilitation purposes have been acknowledged since the first report of this phenomenon (Collins et al. 2001). Such enthusiasm has, however, been dampened by the large inter-individual variability observed in evoked force magnitude in response to WPHF NMES (Neyroud et al. 2014, 2016, 2018; Wegrzyk et al. 2015). Further, if it is clear that responders should be differentiated from non-responders, it remains unknown whether non-responders might start to develop extra forces with repeated application of WPHF NMES. Based on the present results, it appears that non-responders can actually become responders over the course of a 3-week WPHF NMES training program of nine sessions. If only three participants belonging to the training

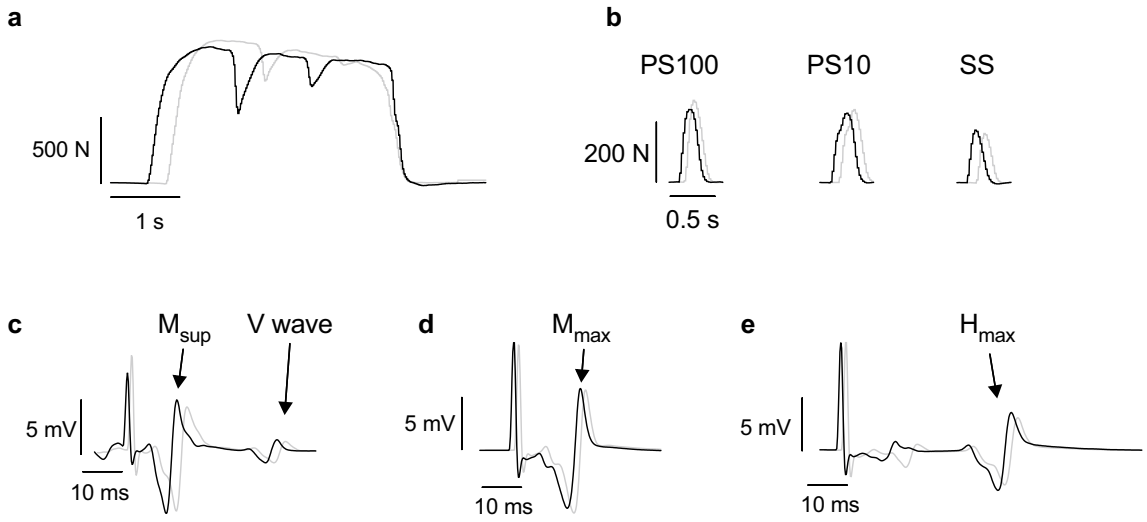

Fig. 6 Typical traces of plantar flexor neuromuscular properties recorded before and after the 3-week WPHF NMES training program. Typical traces of **a** maximal voluntary contraction (MVC) forces and **b** 100-Hz (PS100), 10-Hz (PS10) and single stimulation (SS)-evoked force responses recorded at the beginning of the first (black) and last (grey) training sessions. Panels **c**–**e** represents *soleus* superimposed M wave and V reflex (**c**), maximal M wave (M_{max}, **d**) and maximal H reflex (H_{max}, **e**)

group appeared to produce extra forces at session 1 (i.e., T2, T3 and T8), two additional participants (T7 and T9) could also be classified as responders during the last training session (empty circle for session 1 vs. filled triangle for session 9 in Fig. 4b). This shift of responder status was not seen in the control group (i.e., none of the non-responders became responders in session 9, Figs. 3, 4). It is also interesting to note that two participants (T2 and T3) who were initially responding to WPHF NMES, appeared to respond even more after training as highlighted by an increase in the final (+14 and +102% for these two individuals, respectively) and mean (+13 and +97%, respectively) evoked forces. Further, the majority of the participants showed greater evoked forces as the training program progressed (Fig. 5). Moreover, during some of the contractions, some participants who were classified as non-responders both before and after the training program showed large increases in evoked forces during the last training session (e.g., T5 and T6, Fig. 2). Overall, it appears that non-responders might turn into responders with repeated exposure to WPHF NMES with a potential strengthening of the neural circuitry responsible for extra-force development.

Based on the mechanisms previously hypothesized to account for differences in extra-force development during WPHF NMES (Bergquist et al. 2011), our training program might have (1) strengthened the large diameter afferent—α-motoneuron connections, (2) increased monoamine levels at the spinal level, (3) increased persistent inward currents (which allow neurons to fire independently of neuronal input), (4) increased corticospinal excitability and/or (5) released some unconscious mechanisms related to stimulation apprehension that may have inhibited force development during the first session(s). For instance, an acute WPHF NMES session has been shown to induce both spinal and supraspinal adaptations (Gueugneau et al. 2017; Grospretre et al. 2017; Wegrzyk et al. 2017; Mang et al. 2010). Yet, as previously mentioned, no changes in the H_{max}/M_{max} or V/M_{sup} ratios were found following the 3-week training period. Nevertheless, despite this absence of changes, the fact that some participants became responders after the 3-week training period and showed a slight, even though non-significant, increase in sustained EMG activity suggests that some neural adaptations [e.g., development of persistent inward current (Heckmann et al. 2005)] could actually have occurred.

Overall, these results suggest that WPHF NMES training might potentially be of interest. However, further studies are required to optimize the frequency and duration of the training program/session as well as the stimulation intensity at which WPHF NMES should be delivered. It can be speculated that a longer training period might be effective to increase MVC force (by promoting neural adaptations). The first couple of weeks may serve to 'set up' the neural circuitry responsible for extra-force development by strengthening it through repeated WPHF stimulations until extra-force development occurs. Thereafter, during the subsequent weeks of the training program, the extra-force associated with WPHF NMES would result in an increased force level that may in turn promote an increase in MVC force. However, it should be investigated how to optimally set the stimulation intensity based on individual responses throughout the training period (i.e., how to minimize fatigue

and antidromic collisions in motor axons while maximizing extra-force development).

Limitations

The present results should be interpreted with the following limitations in mind. First, no participant selection was performed beforehand (i.e., to only include those showing extra-force development) as it was unknown whether non-responders might become responders with repeated application of WPHF NMES. Second, the participants involved in the present training study were all physically active individuals and as such the room for training-induced adaptations was smaller than that in a detrained clinical population. It thus remains unknown whether increases in WPHF NMES-evoked forces such as those reported here could result in strength gains in frail individuals (Kraemer and Ratamess 2004). Indeed, classical NMES delivered at very low intensity (motor threshold) is beneficial to critically ill patients as highlighted by increased voluntary force and preservation of muscle mass (see (Maffiuletti et al. 2013; Burke et al. 2016) for review). Third, it is possible that a longer training program (more than 3 weeks) and/or higher training volume per session (more than 10 contractions) would allow participants to progressively develop greater evoked forces and as a result greater neuromuscular adaptations. Fourth, even though WPHF stimulation intensity should remain low to prevent antidromic collision and maximize extra-force development (Bergquist et al. 2011), a slightly higher initial evoked force might be considered in future studies (e.g., 10–15% MVC). Lastly, further studies directly comparing neuromuscular adaptations induced by classical NMES vs. WPHF NMES training are required to better understand the real potential of WPHF NMES as a functionally and clinically relevant strategy for strength training and rehabilitation.

Perspectives

Despite the lack of significant effects of WPHF NMES training on MVC force, we observed a significant increase in WPHF NMES-evoked forces over a 3-week WPHF NMES program. As in frail population even a weak stimulus can improved muscle strength, the present results might open new perspectives for rehabilitation. The mechanisms underlying the training-induced increase in evoked force as well as the potential functional implications remain to be investigated before any potential clinical application of WPHF NMES can be considered.

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Author contributions DN and NP conceived and designed the experiment. DN, MG, SM, DA and NP conducted experiments. DN, MG, SM and DA took part in data analysis. All authors were involved in data interpretation. DN wrote the manuscript. All authors read and approved the manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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