Eur J Appl Physiol (2011) 111:2409–2426
DOI 10.1007/s00421-011-2087-9

MINI REVIEW

Neuromuscular electrical stimulation: implications of the electrically evoked sensory volley

A. J. Bergquist · J. M. Clair · O. Lagerquist · C. S. Mang · Y. Okuma · D. F. Collins

Received: 16 February 2011 / Accepted: 11 July 2011 / Published online: 30 July 2011

Abstract Neuromuscular electrical stimulation (NMES) generates contractions by depolarising axons beneath the stimulating electrodes. The depolarisation of motor axons produces contractions by signals travelling from the stimulation location to the muscle (*peripheral* pathway), with no involvement of the central nervous system (CNS). The concomitant depolarisation of sensory axons sends a large volley into the CNS and this can contribute to contractions by signals travelling through the spinal cord (*central* pathway) which may have advantages when NMES is used to restore movement or reduce muscle atrophy. In addition, the electrically evoked sensory volley increases activity in CNS circuits that control movement and this can also enhance neuromuscular function after CNS damage. The first part of this review provides an overview of how *peripheral* and *central* pathways contribute to contractions evoked by NMES and describes how differences in NMES parameters affect the balance between transmission along these two pathways. The second part of this review describes how NMES location (i.e. over the nerve trunk or muscle belly) affects transmission along *peripheral* and *central* pathways and describes some implications for motor unit recruitment during NMES. The third part of this review summarises some of the effects that the electrically evoked sensory volley has on CNS circuits, and highlights the need to identify optimal stimulation parameters for eliciting plasticity in the CNS. A goal of this work is to identify the best way to utilize the electrically evoked sensory volley generated during NMES to exploit mechanisms inherent to the neuromuscular system and enhance neuromuscular function for rehabilitation.

Keywords Motor unit recruitment · Electrical stimulation · H-reflex · M-wave · Plasticity · Rehabilitation · Muscle contraction · Central nervous system

Communicated by Roberto Bottinelli.

This article is published as part of the Special Issue Cluster on the XVIII Congress of the InternationalSociety of Electrophysiology and Kinesiology (ISEK 2010) that took place in Aalborg, Denmark on 16–19June 2010.

A. J. Bergquist · J. M. Clair · O. Lagerquist · C. S. Mang · Y. Okuma · D. F. Collins (✉)
Human Neurophysiology Laboratory, Faculty of Physical Education and Recreation, Centre for Neuroscience, University of Alberta, 6-41 General Services Building, Edmonton, AB T6G 2H9, Canada
e-mail: dave.collins@ualberta.ca
URL: http://www.dfcollins.ca

Introduction

Neuromuscular electrical stimulation (NMES) is used to generate contractions for training and rehabilitation. Following damage to the central nervous system (CNS), the electrically evoked contractions can be used to restore purposeful movements (functional electrical stimulation; FES) and can also produce enduring improvements in neuromuscular function that outlast the stimulation (therapeutic electrical stimulation; TES). Much research has been conducted on how different NMES parameters affect the evoked contractions, with a general goal of identifying how best to produce the most fatigue-resistant contractions (Binder-Macleod and Scott 2001; Gregory et al. 2007; Kesar et al. 2007; Gondin et al. 2010). This work has provided important information about generating contractions primarily through *peripheral* pathways (see Fig. 1), as the way in which the NMES has been delivered in most

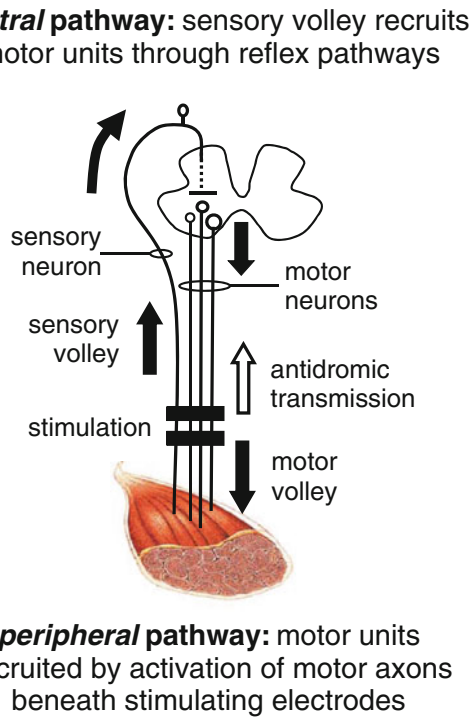

Fig. 1 Schematic of *peripheral* and *central* pathways. Motor units are recruited by the electrically evoked motor and sensory volleys initiated by depolarisation of axons beneath the stimulating electrodes. The contribution from the evoked sensory volley is limited by antidromic transmission in motor axons at high stimulation amplitudes (adapted from Collins 2007)

studies tends to favour the contribution made by activating motor axons. Research in our laboratory has focused on identifying ways of generating contractions through *central* pathways, initiated by the activation of sensory axons (see Collins 2007 for review). Generating contractions through *central* pathways recruits motor units by the synaptic activation of motor neurons (Fig. 1), similar to the recruitment that occurs during voluntary contractions, and this may be beneficial when NMES is used for rehabilitation. Specifically, increasing *central* recruitment during NMES may improve the effectiveness with which NMES can reduce muscle atrophy for TES and produce contractions that are more fatigue resistant for FES. Further, the electrically evoked sensory volley increases activity in CNS circuits that control movement and this can also help in the recovery and enhancement of neuromuscular function after CNS damage. We have found that manipulating not only the NMES parameters (i.e. pulse amplitude, duration and frequency), but also the location for delivery of NMES (i.e. over the nerve trunk or muscle belly) can alter the electrically evoked sensory volley and its influence on muscle contractions and CNS circuits. The first part of this review article describes how transmission along motor and sensory pathways contributes to contractions generated during NMES. We describe the effect of changing stimulation parameters on the balance between the contribution made by transmission along *peripheral* and *central* pathways. In the second part of this review, we describe the effect of NMES location on electrically evoked contractions and discuss some implications of this for using NMES for rehabilitation. The third part of this review focuses on how the electrically evoked sensory volley influences the excitability of CNS circuits. We describe the effect of manipulating NMES parameters on corticospinal (CS) excitability and discuss some of the challenges associated with trying to identify the best way to apply NMES to increase excitability and strengthen CS pathways for rehabilitation. A goal of this research is to identify how best to utilize the electrically evoked sensory volley to take advantage of mechanisms inherent to the neuromuscular system and enhance neuromuscular function for rehabilitation.

NMES and the *central* recruitment of motor units

NMES generates contractions by the repetitive depolarisation of axons beneath the stimulating electrodes. The depolarisation of motor axons produces contractions by signals travelling from the stimulation location to the muscle (*peripheral* pathway), with no involvement of the CNS (motor volley; Fig. 1). Motor units recruited through this pathway discharge relatively synchronously, and their discharge can be measured as an M-wave in the electromyographic (EMG) signal recorded from the muscle innervated by the stimulated nerve as can be seen in the EMG traces in Fig. 2. In the same way that motor axons are recruited during NMES, sensory axons are also depolarized (sensory volley; Fig. 1). The resultant sensory volley comprises signals in afferents from muscle spindles, Golgi tendon organs and cutaneous receptors (Burke et al. 1983). This sensory volley is sent to the CNS relatively synchronously, compared to sensory feedback generated during voluntary movements. It has been estimated that when evoked by electrical stimulation of the tibial nerve trunk in the popliteal fossa, signals in the fastest conducting Ia afferents arrive at the motor neuron in $\sim$15 ms, with the slowest arriving 6.7–9.4 ms later (Burke et al. 1983). The amount of temporal dispersion of the sensory volley will depend on the distance between the stimulating electrodes and the spinal cord, with less dispersion for more proximal locations. During NMES, the sensory volley is sent to the CNS repetitively at the frequency of stimulation, and can contribute to the electrically evoked contraction by the synaptic recruitment of neurons in the spinal cord (*central* pathway; Fig. 1). Thus, contractions produced by NMES can be generated by a combination of *peripheral*

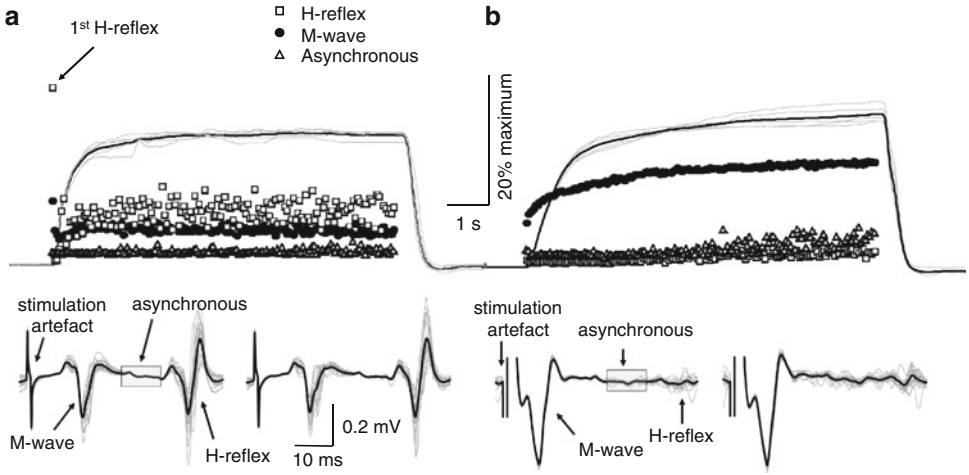

Fig. 2 Torque and soleus EMG evoked by 20 Hz NMES delivered over the tibial nerve trunk (**a**) and TS muscle belly (**b**) in a single participant. In the upper half of each panel, torque represented by the *black lines* are average responses to five trains of NMES (*grey lines*) and the *symbols* represent the average EMG data over five repetitions during a single trial. Vertical calibration represents 20% M_{max} for EMG and 20% MVC for torque. The lower half of each panel shows EMG traces recorded over a 1-s period at 2–3 s into the stimulation (*left trace*) and 6–7 s into the stimulation (*right trace*) during a single train of NMES. *Bold black lines* represent the average of 20 single responses (*grey lines*) to NMES. All data are shown on the same scale, as indicated by the calibration *bars* in **a** (adapted from Bergquist et al. 2011)

recruitment, by the activation of motor axons beneath the stimulating electrodes, and *central* recruitment, by the electrically evoked sensory volley. Confirmation that the *central* recruitment of motor units contributes to electrically evoked contractions has been provided by experiments in which NMES was applied before and during a complete anaesthetic block of the peripheral nerves between the stimulation location and the spinal cord (Collins et al. 2001, 2002a; Blouin et al. 2009; Lagerquist et al. 2009). In these experiments, contractions were larger before the nerve block, when the CNS could contribute to the electrically evoked contraction, than during the nerve block when only transmission along *peripheral* pathways could contribute. Thus, during NMES the recruitment of motor units through *central* pathways can augment contractions generated through *peripheral* pathways, leading to the development of greater torque (*extra* or *central* torque). A *central* contribution to electrically evoked contractions has now been shown for the triceps surae (TS) (Collins et al. 2002a; Baldwin et al. 2006; Klakowicz et al. 2006; Bergquist et al. 2011), tibialis anterior (TA) (Collins et al. 2002a; Klakowicz et al. 2006), quadriceps (Bergquist et al., in revision), wrist extensors (Baldwin et al. 2006) and flexor pollicis longus (Blouin et al. 2009). The strength of the *central* contribution, measured as the amplitude of H-reflexes, asynchronous activity (see below) and evoked torque, depends on the muscle being stimulated, the stimulation parameters (Collins et al. 2002b; Dean et al. 2007; Lagerquist et al. 2009) and the stimulation location (Baldwin et al. 2006; Bergquist et al. 2011; Bergquist et al., in revision). We have noticed anecdotally that there are large and reproducible differences between individuals regarding the extent to which transmission through *central* pathways can contribute to the evoked contraction (unpublished observation); further study regarding the mechanisms that underlie these individual differences is warranted, however, we have speculated that they may be due, in part, to differences in the level of monoamines in the spinal cord (Collins 2007). Additionally, caution must be taken when evoked torque is the only measure for assessing the extent of transmission through *central* pathways (i.e. when EMG is not recorded concurrently), as small nonlinearities in torque production can be evoked in isolated muscle (Binder-Macleod and Clamann 1989; Frigon et al. 2011).

The sensory volley generated during NMES recruits motor units *centrally* in two distinct ways. Perhaps the most obvious form of *central* recruitment is through the Hoffmann- or H-reflex pathway (Klakowicz et al. 2006; Bergquist et al. 2011; Lagerquist and Collins 2010). Like the M-wave, motor units recruited through H-reflex pathways discharge relatively synchronously although at a longer latency, as seen in the EMG traces in Fig. 2a, due to a longer pathway through the spinal cord. Thus far, electrically evoked contractions with a robust contribution from H-reflexes have been shown for the TS (Fig. 2a) (Klakowicz et al. 2006; Bergquist et al. 2011; Lagerquist and Collins 2010) and quadriceps (Bergquist et al., in revision). In some individuals, contractions that generate 30–40% of the torque generated during a maximum voluntary contraction (MVC) could be produced almost exclusively by H-reflexes in both muscle groups. On the

contrary, the H-reflex contribution to electrically evoked contractions of TA is small (Klakowicz et al. 2006) consistent with the weaker reflexive inputs to TA motor neurons (Jusic et al. 1995). The second form of *central* recruitment that occurs during NMES results in motor unit discharge that, unlike the M-wave and H-reflex, is not synchronized to each stimulus pulse (Lang and Vallbo 1967; Collins et al. 2001; Bergquist et al. 2011). Such asynchronous activity tends to develop over time and generates contractions that are qualitatively similar to contractions that develop during tonic vibration reflexes, which arise when vibration is applied over a tendon or muscle belly (Hagbarth and Eklund 1966; Burke and Schiller 1976; Magalhaes and Kohn 2010). This type of motor unit discharge may be due to pre-synaptic mechanisms, such as post-activation potentiation of neurotransmitter release and/or post-synaptic mechanisms, such as the activation of persistent inward currents in spinal neurons (Collins et al. 2001, 2002b). Asynchronous activity can be observed in single motor unit recordings (Collins et al. 2001) and using surface EMG, where it appears as an increase in baseline activity measured between the M-wave and the H-reflex (Bergquist et al. 2011), as is evident after the M-wave in the EMG recording at the bottom of Fig. 2b.

Effect of NMES parameters on *central* recruitment

The following sections provide an overview of how NMES pulse amplitude, duration and frequency influence the electrically evoked sensory volley and the recruitment of motor units through *central* pathways.

Pulse amplitude

Increasing the amplitude of NMES pulses (i.e. current or voltage) produces a stronger depolarizing drive that travels deeper into the underlying tissue (Theurel et al. 2007; Mesin et al. 2010). Clearly, higher amplitude NMES generates larger contractions by depolarizing more motor axons beneath the stimulating electrodes. Higher amplitude NMES will also depolarize more sensory axons and send a larger sensory volley into the CNS, however, the extent to which this larger sensory volley can contribute to the evoked contraction is limited by antidromic transmission in motor axons (Fig. 1). At high NMES amplitudes, antidromic transmission in motor axons blocks orthodromically transmitted signals, reducing the extent to which the *central* recruitment of motor units can contribute to electrically evoked contractions (Gottlieb and Agarwal 1976; Pierrot-Deseilligny and Mazevet 2000). Thus, contractions evoked at maximal amplitudes, that activate all the motor axons to a given muscle, will be driven exclusively by activity through *peripheral* pathways. Generating contractions with a large *central* contribution requires that the stimulation be delivered at a low enough amplitude to minimize this antidromic block. In some individuals, NMES (100 Hz) delivered at or near motor threshold, when there is little or no antidromic block in motor axons, can generate up to 40% MVC torque almost exclusively through *central* pathways (Collins et al. 2001, 2002b; Collins 2007). On average across a group of 5 participants, when NMES was applied over the tibial nerve trunk to evoke plantarflexion contractions of ~25% MVC torque, soleus M-waves and H-reflexes were ~5 and 10% the size of a maximal M-wave (M_{max}), respectively (Bergquist et al. 2011). Across a group of eight participants, NMES over the femoral nerve trunk to produce knee extension contractions of 20% MVC torque was generated by M-waves and H-reflexes in vastus lateralis and vastus medialis that were ~11% M_{max} (Bergquist et al., in revision).

Overall, to evoke contractions with a large *central* contribution for FES, the stimulation amplitude must be delivered low enough to minimise antidromic block, but contractions must be large and stable enough to be useful for restoring movement. Whether these criteria will be met for restoring movement in populations with CNS damage requires further investigation. For TES, when contraction stability is less of an issue, generating contractions through *central* pathways may prove to be an effective way to reduce muscle atrophy and improve muscle quality.

Although delivering NMES at lower amplitudes may seem counter-intuitive when considering that benefits derived from NMES training tend to be proportional to the NMES contraction amplitude (intensity, Selkowitz 1985; dose, Stevens et al. 2004), high contraction amplitudes can be problematic for people with hyper-sensitivity (Sheffler and Chae 2007) or who have compromised bone density (Dudley-Javoroski and Shields 2008). Whether delivering the NMES at lower amplitudes to enhance *central* recruitment can parallel some of the impressive training results obtained at high contraction amplitudes, such as those by Gondin et al. (2011), who report improvements in muscle mass, maximal voluntary strength, neural drive, oxidative metabolism and antioxidant defence system following 8 weeks of NMES training at contraction amplitudes of ~55–60% MVC requires further investigation. However, delivering the NMES at lower amplitudes to enhance *central* recruitment may at the very least increase participation in NMES programs, as many people do not participate due to discomfort associated with the stimulation.

Pulse duration

Changing the duration of the pulses delivered during NMES alters the relative recruitment of motor and sensory axons. Short pulse durations (0.05–0.4 ms) preferentially activate motor axons (Grill and Mortimer 1996), whereas

the use of longer pulse durations (0.5–1 ms) will recruit relatively more sensory axons (Kiernan et al. 1996; Mogyoros et al. 1996; Hugon 1973; Panizza et al. 1989). This differential effect of pulse duration on axonal recruitment is related to sensory axons having a longer strength-duration time constant and lower rheobase than motor axons (Veale et al. 1973; Panizza et al. 1992) and is the reason that longer pulse durations are more effective for evoking the H-reflex (Panizza et al. 1989; Lagerquist and Collins 2008). When single pulses were delivered to the tibial nerve trunk to generate soleus M-wave-H-reflex recruitment curves, the H-reflex recruitment curve was shifted to the left, relative to the M-wave recruitment curve, when using longer pulse durations (0.5 and 1 ms vs. 0.05 ms), consistent with a preferential recruitment of sensory over motor axons. Accordingly, when the M-wave was 5% $M_{max,}$ H-reflexes were significantly larger when using longer pulse durations compared to shorter pulse durations (Lagerquist and Collins 2008).

A similar effect of pulse duration, consistent with changes in the relative recruitment of sensory and motor axons, occurs during repetitive stimulation (NMES). During NMES at 100 Hz over the TS muscle belly, 1 ms pulses generated significantly larger contractions, indicative of a greater *central* contribution, compared to NMES delivered using 0.05 or 0.25 ms pulse durations, as shown for one participant in Fig. 3a (Collins et al. 2002a). In these experiments the current delivered was adjusted for each pulse duration to evoke the same torque at the beginning of each contraction. In the same study, changing stimulus pulse duration did not alter the *central* contribution to contractions evoked by stimulation over TA (Collins et al. 2002a). A more detailed investigation that included assessment of M-waves, H-reflexes and torque during NMES over the tibial nerve trunk (Lagerquist and Collins 2010) confirmed that additional torque generated by the longer pulse duration was associated with greater *central* recruitment. When NMES was delivered at motor threshold and to evoke an M-wave that was 5% M_{max}, pulse durations of 0.2, 0.5 and 1 ms generated larger H-reflexes and greater torque than a shorter pulse duration (0.05 ms) (Lagerquist and Collins 2010). This effect of pulse duration is shown for one participant in Fig. 4 where H-reflexes and torque were larger following a period of 100 Hz stimulation when NMES was delivered using 1 ms pulses compared to 0.05 ms pulses. Interestingly, M-wave amplitude also depended upon pulse duration. After the initial response, M-waves were depressed when NMES was delivered using 1, 0.5 and 0.2 ms but not 0.05 ms pulse durations. Thus, the use of longer pulse durations during NMES can enhance *central* recruitment and reduce *peripheral* recruitment during NMES.

Pulse frequency

The frequency at which individual pulses are delivered within a NMES train determines the frequency at which action potentials travel along motor and sensory axons. For contractions generated through *peripheral* pathways, pulse frequency influences how force generated through successive M-waves summates and contributes to the smoothness and strength of the evoked contraction. In general, for contractions generated through *peripheral* pathways, NMES is delivered at frequencies high enough to produce fused contractions (20–40 Hz) (Baker et al. 2000; Bigland-Ritchie et al. 2000), but not so high (≥60 Hz) that contractions fatigue rapidly (Gregory et al. 2007; Kesar et al. 2007). This decline in torque at higher pulse frequencies is consistent with our observation that torque tends to decline when NMES is applied at 100 Hz during a peripheral nerve block, when only *peripheral* pathways can contribute (Lagerquist et al. 2009). In the same study, however, significantly more torque was recorded when the same stimulation was delivered before the nerve block, when *central* pathways could contribute.

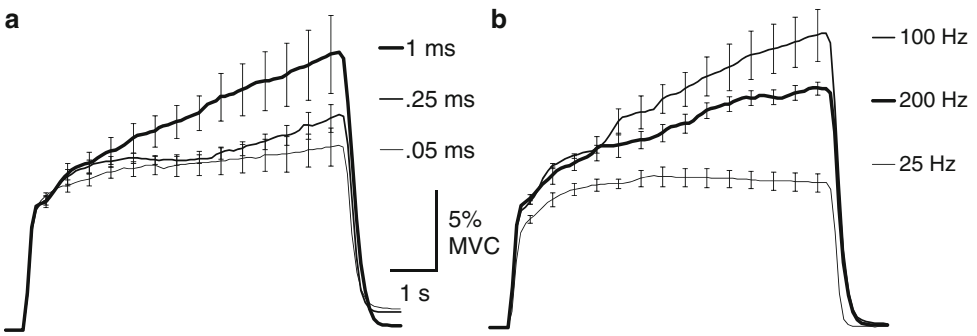

Fig. 3 The effect of pulse duration and pulse frequency on the *central* contribution to electrically evoked contractions of the plantarflexors by NMES delivered over the TS muscle belly. **a** Mean ($n = 5$) torque responses evoked by NMES (100 Hz) using pulse durations of 0.05, 0.25 and 1 ms in a single participant. **b** Mean ($n = 5$) torque responses evoked by NMES (1 ms) using pulse frequencies of 25, 100 and 200 Hz. *Error bars* represent one standard error (adapted from Collins et al. 2002a)

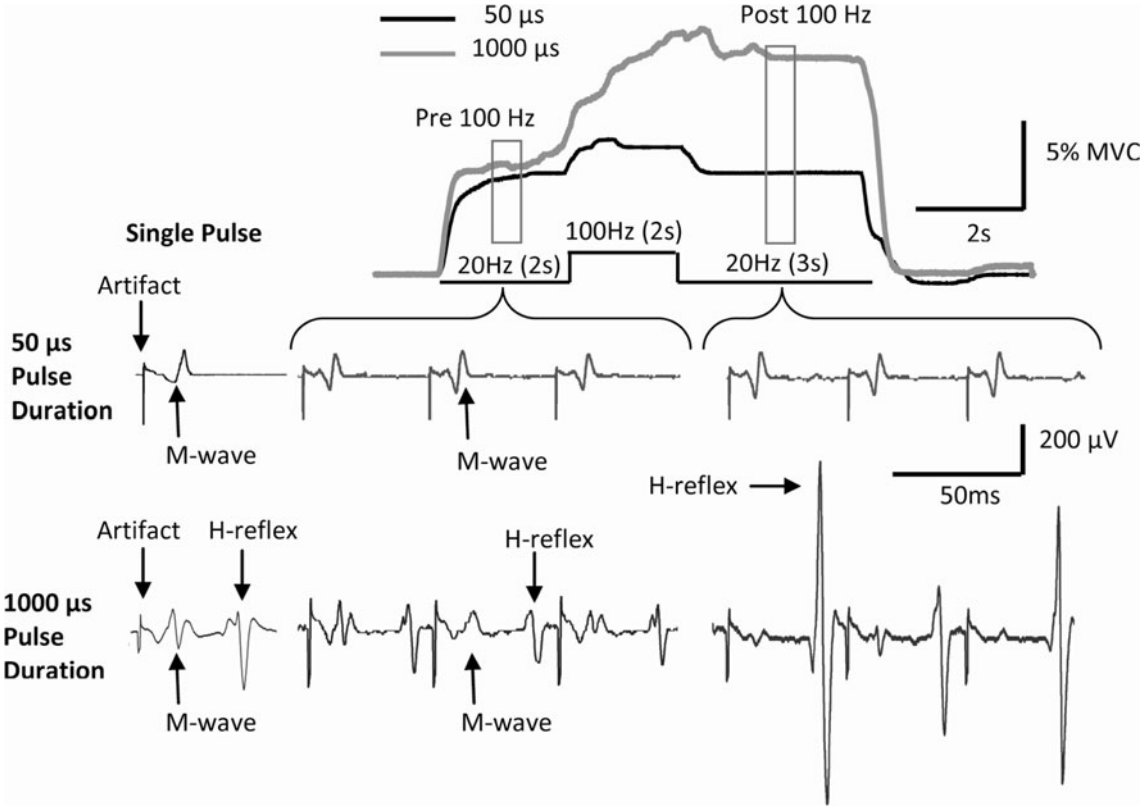

Fig. 4 Plantarflexion torque and soleus EMG evoked by NMES delivered at motor threshold over the tibial nerve trunk in a pattern (20–100–20 Hz for 2–2–3 s, respectively). *Vertical rectangles* indicate the region from which torque and H-reflex data were sampled. A sample of soleus EMG for each pulse duration is displayed beneath the parentheses. Following NMES at 100 Hz, torque and H-reflexes were enhanced when using a 1-ms pulse duration, but not when using a 0.05-ms pulse duration (adapted from Lagerquist and Collins 2010)

The influence of pulse frequency on the recruitment of motor units through *central* pathways can be complicated, as transmission across *central* synapses is strongly dependent upon the frequency of the sensory volley. For example, as pulse frequency increases, H-reflexes are progressively depressed due to post-activation depression of synaptic transmission (Burke and Schiller 1976; van Boxtel 1986; Crone and Nielsen 1989; Schindler-Ivens and Shields 2000). Such post-activation depression is clearly demonstrated during NMES at 20 Hz for a single participant in Fig. 2a (open squares) and for a group of participants in Fig. 5 (filled triangles); both Figures show that soleus H-reflexes remained markedly depressed throughout the NMES train after the first H-reflex. In contrast, Fig. 5 shows that H-reflex amplitude did not change when NMES was delivered at 5 Hz (Fig. 5; Clair et al. 2011), but during 10 Hz NMES reflexes were initially depressed and then their amplitude recovered completely by the end of the stimulation. Interestingly, the amount of reflex depression depended strongly on the voluntary contraction level and depression was greatest when participants were relaxed and was absent during contractions of 20%MVC (Clair et al. 2011). In an apparent contradiction to this frequency-dependant depression of H-reflex transmission, when NMES is delivered over the TS muscle belly at high, but not low, frequencies for several seconds, large contractions can develop (Collins et al. 2001, 2002a). This is shown for a single participant in Fig. 3b where torque increased the most when the stimulation was delivered at 100 Hz compared to NMES at 25 or 200 Hz. Across a group of six participants in this study, torque increased similarly during NMES at 100 and 200 Hz, but did not increase during NMES at 25 Hz. Although measuring H-reflexes or asynchronous activity at such high frequencies is difficult due to contamination of the EMG by successive stimulus artefacts, the large contractions that can develop through *central* pathways (up to 40% MVC) during high frequency stimulation (Collins et al. 2002a) may be due to the emergence of asynchronous activity, as occurs during tonic vibration reflexes (Magalhaes and Kohn 2010).

In addition to the *central* recruitment that can develop during constant high frequency stimulation, *central* recruitment can be augmented when brief periods of high frequency stimulation (bursts) are delivered during longer trains at lower pulse frequencies (Collins et al. 2001, 2002a; Klakowicz et al. 2006; Dean et al. 2007; Bergquist

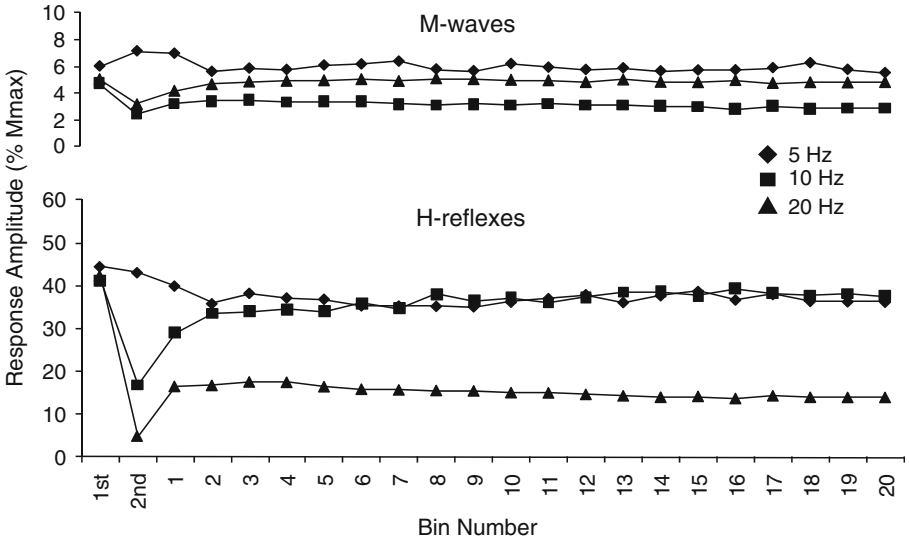

Fig. 5 The effect of pulse frequency on the *central* contribution to electrically evoked contractions of the plantarflexors. Group data ($n = 11$) depicting recovery of H-reflexes during NMES (to evoke an M-wave of ~5% M_{max}) delivered over the tibial nerve trunk at 5, 10 and 20 Hz while seated participants held plantarflexion contractions of 12 ± 4% MVC. The first two pulses are an average of three responses from each participant. The subsequent bins represent data averaged over 0.5 s intervals (adapted from Clair et al. 2011)

et al. 2011; Lagerquist and Collins 2010). Figure 4 shows that both H-reflexes and torque can be augmented after brief bursts of 100 Hz stimulation. These *central* contractions depend on the burst frequency, and are largest at pulse frequencies greater than or equal to 80 Hz (Dean et al. 2007). Taken together these experiments suggest that activity through *central* pathways can contribute to electrically evoked contractions across a range of pulse frequencies, but that the *central* contribution may be predominantly due to H-reflexes at lower frequencies and asynchronous activity when NMES is delivered at higher frequencies, although H-reflexes can be augmented by brief bursts of high frequency (100 Hz) NMES. Thus, delivering NMES that incorporates such bursts into NMES at lower frequencies may be one way to augment *central* recruitment while minimizing the decline in torque associated with motor unit recruitment mediated only through *peripheral* pathways at constant high frequencies (Lagerquist et al. 2009). Differences in the contribution of H-reflexes and asynchronous activity to electrically evoked contractions when NMES is applied over a nerve trunk versus a muscle belly are described further below. The ways in which the aforementioned stimulation parameters affect transmission along *central* pathways for these two stimulation locations are summarised in Table 1.

Recruitment during NMES over a nerve trunk versus a muscle belly

Although NMES can be applied through electrodes implanted under the skin, NMES is typically delivered through electrodes placed on the skin's surface. Surface NMES can be applied through small electrodes placed over a peripheral nerve trunk, or through larger electrodes placed over a muscle belly. A summary of what we believe to be the strengths and weaknesses of delivering NMES over a nerve trunk versus a muscle belly with regards to accessibility of the stimulation site, electrode susceptibility to movement, contraction reliability as well as stimulation comfort is provided in Table 2. Both locations for delivering NMES generate contractions by depolarizing axons beneath the stimulating electrodes, however, the contribution made by *peripheral* and *central* pathways to motor unit recruitment can be markedly different.

When NMES is delivered at relatively low frequencies (≤20 Hz), over the nerve trunk or muscle belly, contractions can develop through different pathways. NMES over the tibial nerve trunk at 20 Hz can be generated with a robust contribution from H-reflexes (Klakowicz et al. 2006; Bergquist et al. 2011). Plantarflexion contractions of ~20% MVC torque can be accompanied by relatively small M-waves, large H-reflexes and little to no asynchronous activity as shown in Fig. 2a. In contrast, when NMES is delivered at 20 Hz over the muscle belly to generate the same torque, contractions are generated predominantly through *peripheral* pathways with minimal *central* recruitment, as demonstrated by large M-waves and minimal H-reflexes and asynchronous activity in Fig. 2b. Of the muscle groups studied thus far, this effect of stimulation location on the *peripheral* and *central* recruitment of motor units have been found for TS (Bergquist et al. 2011) and the quadriceps (Bergquist et al., in revision). In TA, a muscle with relatively weak H-reflexes, dorsiflexion torque in response to low frequency stimulation over the common peroneal nerve trunk is generated predominately through *peripheral* pathways (Klakowicz et al. 2006), while preliminary data suggest that torque in response to stimulation over the muscle belly is generated in a similar way (Okuma, Bergquist and Collins, unpublished

Table 1 Summary of stimulation parameters which show or enhance transmission through *central* pathways

Over a nerve trunk	Over a muscle belly
Pulse amplitude	
Low (to avoid anti-dromic block)	Low (to avoid anti-dromic block)
Pulse duration	
0.2–1 ms	0.2–1 ms
Pulse frequency	
Low (20 Hz), low with *bursts* (20–100–20 Hz) or High (100 Hz)	Low with *bursts* (20–100–20 Hz) or high (100 Hz)
Train duration	
Short (<2 s) or sustained (>2 s)	Sustained (>2 s)

Table 2 Summary of technical strengths and weaknesses of NMES over the nerve trunk versus the muscle belly of the leg

Over a nerve trunk	Over a muscle belly
Accessibility of stimulation site	
Common peroneal (high)	Tibialis anterior (high)
Tibial (medium)	Triceps surae (high)
Femoral (low)	Quadriceps (high)
Electrode susceptibility to movement	
Common peroneal (low)	Tibialis anterior (low)
Tibial (medium)	Triceps surae (low)
Femoral (high)	Quadriceps (low)
Contraction reliability and consistency	
Common peroneal (high)	Tibialis anterior (high)
Tibial (medium)	Triceps surae (high)
Femoral (low)	Quadriceps (high)
Stimulation comfort at sub-maximal amplitudes	
Common peroneal (high)	Tibialis anterior (medium)
Tibial (low)	Triceps surae (medium)
Femoral (high)	Quadriceps (medium)

observation). However, in some participants, there can be a robust *central* contribution to contractions evoked when NMES is applied over the TA muscle belly or common peroneal nerve trunk (Collins et al. 2002a).

These marked differences between nerve trunk and muscle belly stimulation diminish when NMES is delivered at higher pulse frequencies, as activity through *central* pathways can be enhanced during NMES at both locations by increasing the pulse frequency. During stimulation over the nerve trunk, low frequencies allow for an immediate *central* contribution through H-reflex pathways, and contractions that are sustained over several seconds or have periodic bursts of NMES at high frequencies (100 Hz) can enhance this activity (Klakowicz et al. 2006; Bergquist et al. 2011). To generate contractions with a large *central* contribution during NMES over the muscle belly, the use of high frequencies that are sustained over several seconds delivered constantly or in periodic burst*s* (Collins et al. 2001, 2002a; Dean et al. 2007; Bergquist et al. 2011) are required.

These differences in the way motor units are recruited when NMES is applied over a nerve trunk compared to over a muscle belly must be due to differences in how axons are recruited beneath the stimulating electrodes. During NMES over the nerve trunk, sensory and motor axons are bundled close together, and recruitment occurs based on a combination of axon diameter and distance from the stimulating electrodes. When NMES is delivered over the muscle belly, however, the variability in axon distance from the stimulating electrode is much greater because axons branch diffusely throughout the muscle. This branching, in conjunction with the use of larger electrodes and a greater inter-electrode distance, will activate axons over a far broader spatial distribution resulting in a less synchronous sensory volley arriving at the motor neuron, compared with NMES over the nerve trunk. There are also likely to be considerable differences in the types of afferents that contribute to the sensory volley between stimulation locations. Compared to stimulation over the nerve trunk, activating the muscle through larger electrodes over the muscle belly may activate a greater proportion of cutaneous afferents. Thus, the sensory volley generated during NMES over a nerve trunk is likely to comprise a greater proportion of Ia afferents than NMES over a muscle belly. Although these differences in the temporal dispersion and composition of the sensory volley remain to be confirmed experimentally, they are consistent with the fact that it is much easier to evoke an H-reflex when stimulating over a nerve trunk than over a muscle belly. Maximal H-reflexes from recruitment curves generated by stimulation over a nerve trunk were 60 and 30% of M_{max} for the TS (Bergquist et al. 2011) and quadriceps (Bergquist et al., in revision), respectively, while recruitment curves generated by stimulation over the muscle belly resulted in maximal H-reflexes that were 10% and 3% of M_{max}, respectively.

The following sections discuss some implications of the electrically evoked sensory volley for motor unit recruitment during NMES, and highlight differences in the way motor units are recruited between stimulation locations. Specifically, the implications for orderly, temporal and spatial aspects of motor unit recruitment are addressed. This discussion was prompted in part by ideas presented in a recent review article citing these three aspects of recruitment as factors that limit the efficacy of electrically evoked contractions (Maffiuletti 2010). Here we suggest that generating contractions with a large contribution through *central* pathways may help alleviate these limitations of electrically evoked contractions.

Motor unit recruitment order

When motor units are recruited by voluntary descending drive (Milner-Brown et al. 1973) or reflexive inputs (Henneman 1957), small, fatigue resistant, motor units are recruited first, followed by larger, fast-fatigable, motor units in accordance with Henneman's size principle. This recruitment order is attributed to smaller motor neurons having a higher input resistance, which results in their recruitment at lower synaptic currents (Stotz and Bawa 2001). In contrast to this well-established orderly recruitment during synaptic activation, the data available on motor unit recruitment order during NMES are less consistent (see Gregory and Bickel 2005 for review). Initially, recruitment order was thought to be reversed compared to voluntary contractions, based on experiments involving stimulation of motor axons using implanted electrodes (Gorman and Mortimer 1983; Solomonow 1984) and the idea that axons of larger motor units have lower axonal resistance, making them more easily depolarized by externally applied currents (Blair and Erlanger 1933; Solomonow 1984). While this view has a solid theoretical foundation, how NMES generates contractions in vivo may be quite different. In recent years, it has been suggested that motor unit recruitment during NMES follows the size principle (Knaflitz et al. 1990; Thomas et al. 2002; Mesin et al. 2010) or is random with respect to motor unit type (Gregory and Bickel 2005; Jubeau et al. 2007; Mesin et al. 2010). The general consensus now seems to be that when NMES is delivered through the skin in humans, axonal activation depends both on the distance of the axons from the stimulating electrodes as well as axon diameter. As a consequence, for contractions produced through *peripheral* pathways, there is no clear relationship between recruitment and motor unit type (Adams et al. 1993; Kim et al. 1995; Feiereisen et al. 1997; Gregory and Bickel 2005; Jubeau et al. 2007). Delivering NMES in a way that optimises the sensory volley and produces contractions through *central* pathways is one way to generate contractions that follow the size principle (Buchthal and Schmalbruch 1970; Trimble and Enoka 1991). Electrically evoked contractions that recruit fatigue-resistant motor units first should have benefits for TES, to improve muscle quality, and for FES, to generate functional movements.

Temporal aspects of recruitment

During voluntary contractions, motor units are recruited asynchronously with respect to each other, allowing for fused contractions to be achieved at relatively low firing rates [5–25 Hz (Adrian and Bronk 1929; Baker et al. 2000)]. Such low firing rates reduce the metabolic demand placed on individual motor units (Adams et al. 1993). In contrast, during NMES, motor units discharge relatively synchronously relative to each other, as M-waves, time-locked to each stimulus pulse. Thus, to develop fused contractions of comparable force, higher motor unit discharge rates are required during NMES than voluntary contractions, increasing the metabolic demand with respect to force production (Baker et al. 2000; Vanderthommen et al. 2003). This is particularly true for people with chronic spinal cord injury, whose muscle quality below the level of lesion may be compromised (Burnham et al. 1997; Shields 2002; Jacobs and Nash 2004). Due to the inactivity imposed by the injury, paralysed muscle tends to atrophy and slow motor units take on characteristics of fast motor units (Shields 2002). As a result of this shift in muscle fibre composition (Round et al. 1993; Burnham et al. 1997), higher pulse frequencies ($\sim$40 Hz) tend to be required to generate tetanic contractions in people with chronic spinal cord injury compared to people with an acute spinal cord injury or control participants (Stein et al. 1992; Shields 1995). The requisite of such high firing rates during NMES may be diminished by increasing the contribution to the electrically evoked contractions made by motor unit recruitment through *central* pathways.

During NMES over the nerve trunk, contractions can be generated by the recruitment of motor units through both M-wave (*peripheral*) and H-reflex (*central*) pathways, which occur at different latencies with respect to each stimulus pulse. Motor units recruited as M-waves cannot discharge as H-reflexes in response to the same stimulus pulse, due to the aforementioned antidromic transmission along motor axons. Hence M-waves and H-reflexes represent the activation of separate populations of motor units. As such, generating contractions with a contribution from both M-waves and H-reflexes, an example of which is shown in Fig. 2a, may in effect double the combined motor unit firing rate contributing to the evoked torque, while the actual firing rates of individual motor units remains equal to the pulse frequency. In this way, it may be possible to evoke fused contractions at relatively lower discharge rates of individual motor units, which would reduce the metabolic demand on each unit. Realistically, this would only be achievable across a relatively narrow stimulation amplitude range when both the M-wave and H-reflex are contributing appreciably to the evoked torque.

Perhaps a more practical way to reduce the synchronous motor unit discharge during NMES would be to maximise the asynchronous discharge of motor units. Thus far, such activity has been recorded during NMES of the plantarflexors at 20 Hz when the stimulation was maintained for several seconds (Bergquist et al. 2011). Under similar conditions, asynchronous activity was not present during electrically evoked contractions of the quadriceps (Bergquist et al., in revision). However, as noted in the *Pulse*

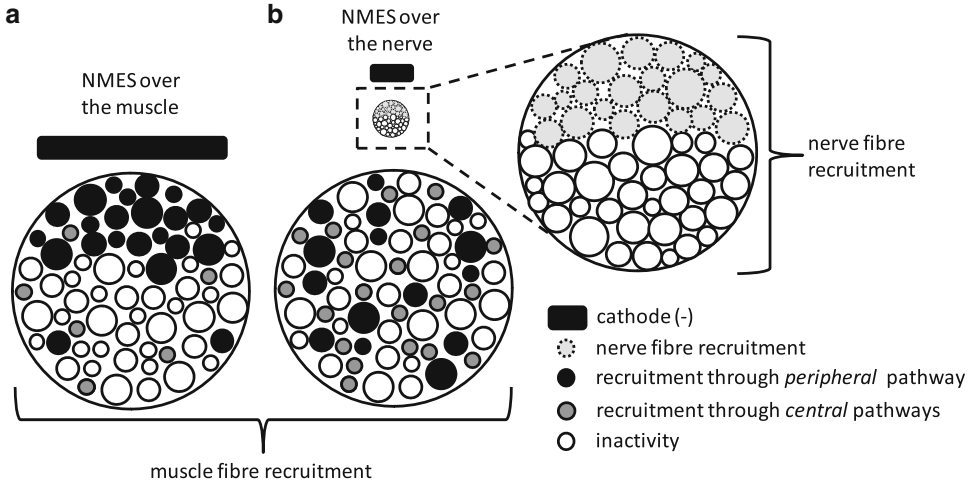

Fig. 6 Proposed spatial recruitment through *central* and *peripheral* pathways. **a** During NMES over a muscle belly, the most superficial muscle fibres are recruited through *peripheral* pathways with limited recruitment through *central* pathways. **b** During NMES over the nerve trunk, both *peripheral* and *central* pathways recruit muscle fibres with a greater spatial distribution, regardless of a superficial recruitment of nerve fibres at the level of the nerve trunk

frequency section (above), higher pulse frequencies may be required to generate significant asynchronous activity. Thus, delivering NMES over the nerve trunk or muscle belly at low amplitudes and high frequencies (100 Hz), at which H-reflexes are substantially depressed, but asynchronous activity is enhanced, may prove to be an effective way to enhance the asynchronous discharge of motor units during NMES.

Spatial aspects of recruitment

Maffiuletti (2010) identified the limited spatial recruitment of motor units as one of the major limitations of NMES. Motor unit recruitment during NMES, at least when applied over the muscle belly, is mainly, but not entirely (Adams et al. 1993), superficial due to the large distance from the stimulating electrodes to the deepest motor units (Vanderthommen et al. 2000; Boerio et al. 2005; Maffiuletti 2010; Mesin et al. 2010; Place et al. 2010). This results in an inability to recruit all of the motor units in a muscle, even at high stimulus amplitudes (Adams et al. 1993; Place et al. 2010). In fact, one estimate suggests that only ~54% of the muscle cross sectional area can be activated during NMES applied over the quadriceps muscles (Adams et al. 1993). This idea of superficial recruitment through *peripheral* pathways during NMES over the muscle belly is depicted schematically in Fig. 6a. To maximise the spatial recruitment of motor units during NMES over the muscle belly, Maffiuletti (2010) has suggested increasing the pulse amplitude, to depolarise additional muscle fibres located at a greater distance from the electrodes (Theurel et al. 2007), and moving the stimulating electrodes or varying joint angle after several contractions, both of which will change the population of superficial fibres that are recruited. We would add that the spatial recruitment of motor units may also be improved upon by maximizing *central* recruitment by stimulating over the nerve trunk or increasing the pulse frequency.

At the level of the nerve trunk, recruitment of motor axons is random in relation to axon diameter and is likely superficial within the nerve trunk (Doherty and Brown 1993; Baker et al. 2000; Major and Jones 2005) as depicted in Fig. 6b. However, due to the diffuse manner in which those axons project from the stimulation location to muscle fibres throughout the muscle belly, one would expect that motor units recruited as M-waves during NMES over the nerve trunk to be evenly distributed throughout the muscle (filled circles; Fig. 6b). This contrasts with the superficial activation of motor units closest to the stimulating electrodes (Vanderthommen et al. 2000) recruited as M-waves during NMES over the muscle belly (Mesin et al. 2010) as depicted in Fig. 6a. Thus, even for contractions produced solely through *peripheral* pathways, stimulation over the nerve trunk is likely to recruit motor units with a wider spatial distribution throughout the muscle.

Generating contractions through a combination of *peripheral* and *central* pathways, regardless of whether the stimulation is applied over a nerve trunk or muscle belly, may also increase the spatial distribution of motor unit recruitment throughout a muscle. As mentioned previously, contractions generated through *central* pathways should follow the size principle and activate fatigue-resistant motor units located throughout the muscle (shaded circles; Fig. 6). The implications of this orderly recruitment through *central* pathways for the spatial recruitment of motor units may be different for different muscle groups. For muscles such as the quadriceps, fatigue-resistant motor units are located in deeper compartments (Lexell et al. 1983; Knight and Kamen 2005), where they are less accessible for activation via NMES over the muscle belly (Vanderthommen et al. 2000; Mesin et al. 2010; Place et al. 2010). Thus generating contractions through both M-waves and H-reflexes would increase the spatial recruitment of motor units due to the different populations of motor units recruited through these different pathways (Buchthal and

Schmalbruch 1970; Trimble and Enoka 1991). For muscles such as TA, however, where fatigue-resistant muscle fibres are located superficially (Mesin et al. 2010), contractions generated through both *peripheral* and *central* pathways with NMES over the muscle belly may tend to recruit muscle fibres in superficial compartments. Thus, producing contractions in part through M-waves evoked by stimulation of the common peroneal nerve trunk may help to activate deeper compartments of the muscle.

Finally, motor unit recruitment during long sub-maximal voluntary contractions can occur with rotation (Bawa et al. 2006). Recruitment with rotation refers to the situation whereby motor units that have been discharging for long periods of time cease firing and are replaced by previously inactive motor units of similar threshold. This increases the spatial distribution of recruitment during voluntary contractions and helps minimise fatigue, while contraction force remains stable (Bawa et al. 2006). Rotation of motor unit recruitment during NMES has not been reported and during NMES over the muscle belly, the same superficial motor units are likely to be continuously activated (Vanderthommen et al. 2000) with no opportunity for rotation to maintain contractile force, because rotation is a property of synaptic recruitment and relies on the gradual increase in the threshold of motor neurons in the spinal cord (Bawa et al. 2006). Whether recruitment with rotation occurs during NMES when motor units are recruited through *central* pathways is not known, although it is tempting to speculate that the *central* recruitment would result in a unique cycling of motor unit recruitment during NMES.

Effect of NMES on CNS circuits

The implications of the electrically evoked sensory volley generated during NMES are not limited to the electrically evoked contractions. In traversing the spinal cord and ascending to the brain, the sensory volley increases activity in spinal and cortical circuits that control movement (Spiegel et al. 1999; Deuchert et al. 2002; Blickenstorfer et al. 2008) and this can lead to both short-term and long-term neuroplasticity. Generally, reducing activity in neural circuits, such as occurs after CNS injury or disease and prolonged disuse, reduces the excitability of CNS circuits and weakens pathways between the brain and muscle (Liepert et al. 2000). Increases in CNS activity, such as occurs when learning a new motor skill (Classen et al. 1998) and during NMES (Liberson et al. 1961; Hamdy et al. 1998; Ridding et al. 2000), increases the excitability of the same CNS circuits and strengthens CS pathways. Currently, an active area of research is focused on developing a better understanding of how NMES alters activity in CNS circuits. This work will provide a foundation upon which to develop better ways to use NMES for rehabilitation to promote neuroplasticity that leads to improvements in neuromuscular function.

The idea that NMES can lead to enduring improvements in neuromuscular function is not new, but has its roots in some of the original FES research. Liberson et al. (1961) noted that when NMES was applied over TA to improve dorsiflexion during the swing phase of locomotion, improvements could outlast the FES sessions, implying that some kind of CNS adaptation had occurred. Evidence that NMES can induce measurable changes in CNS circuits came some time later, when Hamdy et al. (1998) showed that 10 min of NMES of the pharyngeal nerve increased CS excitability and reorganized cortical maps for the muscles that control swallowing. Subsequently, lasting changes in CS excitability and cortical reorganization following NMES have been reported for a variety of limb muscles including first dorsal interosseus (Ridding et al. 2000; Pitcher et al. 2003), abductor pollicis brevis, abductor digiti minimi (Ridding et al. 2000), and TA (Khaslavskaia et al. 2002; Knash et al. 2003). Like the plasticity associated with learning a new task, increases in excitability induced by NMES can last for ~5 min to 1 h after a single session, and for as long as 2 days when NMES is applied on successive days (McKay et al. 2002a, b). The following sections review some of the mounting evidence that NMES can increase CNS excitability. We also introduce some data we have collected to begin to identify optimal NMES parameters for inducing such changes and to compare the effects of NMES on increasing CS excitability for muscles of the arms and legs.

NMES and spinal circuits

Much of the research designed to identify the influence of NMES on CNS circuits has focused on pathways between the brain and skeletal muscles. However, it is clear that both short- and long-term changes can occur in the excitability of spinal pathways (see Field-Fote 2004 for review). As described in *Pulse frequency* (above; see Figs. 4, 5), transmission along the H-reflex pathway is frequency dependent and can be facilitated or inhibited depending on the frequency of the sensory volley (van Boxtel 1986). While frequency-dependent facilitation or inhibition provide examples of short-term changes in transmission through spinal pathways during the stimulation, NMES can also lead to enduring changes in the excitability of spinal circuits that persist after the stimulation is turned off. For example, NMES can lead to long-term increases in reciprocal inhibition (Perez et al. 2003) and this may restore levels of reciprocal inhibition that have weakened due to prolonged disuse (Crone et al. 1994; Thompson et al. 2009). NMES can also influence neural circuits controlling

muscles contralateral to the stimulation. This cross-education phenomena, where training of a muscle group on one side of the body can enhance the performance of the same muscle group on the contralateral side, is particularly potent during NMES-induced training, compared with voluntary training, and is thought to be mediated by activation of Group II muscle afferents (Hortobagyi et al. 1999; Maffiuletti et al. 2006). The extent to which NMES alters transmission along spinal circuits merits further investigation. However, it is clear that NMES can induce activity-dependent changes in spinal circuits and this may hold promise for reversing changes that occur in spinal pathways due to disuse, by increasing activity in these pathways through the electrically evoked sensory volley.

NMES and cortical circuits: stimulation parameters and CS excitability

The most common way to assess the effect of NMES on the excitability of CS pathways is to apply transcranial magnetic stimulation (TMS) over the motor cortex to generate motor evoked potentials (MEPs) in specific muscles before and after an NMES session. Although MEP amplitude can be influenced by the excitability of cortical and spinal circuits, there is evidence that changes in CS excitability evoked by NMES are mediated primarily at the level of the motor cortex (Ridding et al. 2000; Khaslavskaia et al. 2002). Regardless, enduring increases in CS excitability measured using TMS, which reflect a strengthening of CS pathways, are often associated with improvements in functional outcomes of movement rehabilitation programs (Conforto et al. 2002; Kido and Stein 2004; Stein et al. 2010; Everaert et al. 2010).

When NMES is used to increase CS excitability, the parameters of stimulation have varied widely. To increase CS excitability for leg muscles, NMES is typically applied using stimulation amplitudes sufficient to generate contractions and produce functional movements (i.e. FES), low frequencies (~10–50 Hz), and short pulse durations (~0.02 ms). In contrast, when NMES is used to enhance CS excitability for muscles in the arm, it is typically applied at low amplitudes (near or below motor threshold), high frequencies (up to 200 Hz), and long pulse durations (up to 1 ms). This type of stimulation is often termed somatosensory stimulation (SS) and is designed to activate primarily sensory axons and prime CNS circuits for rehabilitation sessions, without producing large or functional muscle contractions (Hoffman and Field-Fote 2007). Even between studies that have used FES over leg muscles or SS for hand muscles, many stimulation parameter combinations have been used. For example, in studies investigating the effect of FES on CS excitability for leg muscles, amplitudes have varied from below motor threshold to 50% of a maximal M-wave, frequencies have varied from 1 Hz to 200 Hz, and pulse durations have varied from 0.2 to 1 ms. NMES has also been applied in a variety of different patterns and for differing durations [10 min (Hamdy et al. 1998) to 2 h (Ridding et al. 2000)]. Varying NMES parameters alters the sensory volley transmitted to the CNS and influences how NMES changes CS excitability (Fraser et al. 2002). Unfortunately, the wide range of NMES parameters that have been used to alter CS excitability have made it difficult to compare between studies and identify parameters that may be optimal for increasing excitability the most, the fastest and for the longest duration.

To begin to fill this gap in our knowledge, we investigated how different pulse frequencies delivered over the common peroneal nerve affect CS excitability (Mang et al. 2010). Given that the strength of the sensory volley depends on pulse frequency, we hypothesised that CS excitability would increase more when NMES was applied at higher pulse frequencies. NMES was applied over the common peroneal nerve to activate TA at 10, 50, 100 or 200 Hz in a 20 s on–20 s off pattern for 40 min at an amplitude that evoked an M-wave that was ~5% M_{max}. This protocol was intended to represent one that could be used to generate contractions during an FES rehabilitation session. Consistent with our hypothesis, the 100 Hz NMES increased CS excitability more than NMES at 10 or 50 Hz as shown for one participant in Fig. 7a and this effect was significant across the group as shown by the asterisks in Fig. 7b. NMES at 100 Hz significantly increased MEP amplitude after 24 min (open triangles) compared to MEPs recorded before the NMES session. Contrary to our hypothesis, NMES at 200 Hz was less effective than 100 Hz for increasing CS excitability (not shown; Mang et al. 2010). This optimal effect of 100 Hz stimulation, but not lower or higher frequencies, for increasing CS excitability is similar to the frequency-dependent effect found for maximising motor unit recruitment through *central* pathways during electrically evoked contractions (see Fig. 3b). The weaker effect of NMES at 200 Hz for generating contractions through *central* pathways (albeit non-significant; Collins et al. 2002a) and for increasing CS excitability (Mang et al. 2010) may reflect a decreased ability to activate sensory axons due to activity-dependent hyperpolarisation of the axons beneath the stimulating electrodes (Burke et al. 2001), in which case a weaker sensory volley would be sent to the CNS.

After identifying 100 Hz as an optimal frequency to deliver FES to enhance CS excitability for TA, we then compared this type of NMES with a SS protocol that is commonly used to increase CS excitability for muscles of the hand (Mang, Clair and Collins, unpublished data). Both protocols were delivered over the common peroneal nerve

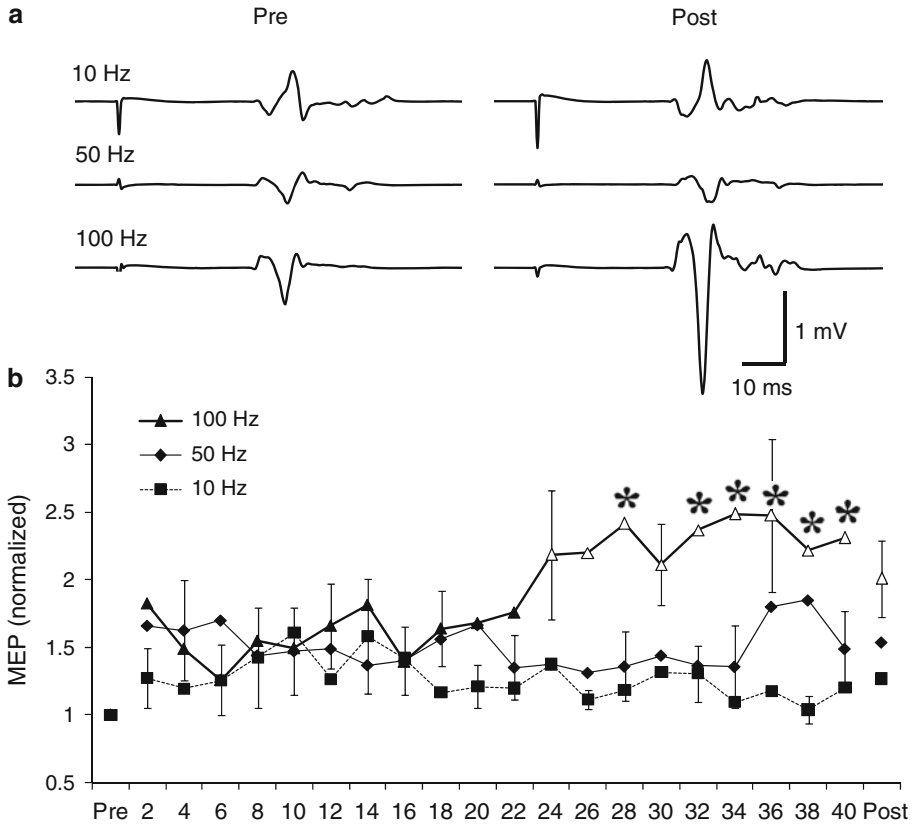

Fig. 7 Frequency dependant changes in CS excitability. **a** Changes in TA MEPs recorded before (pre) and after (post) 40 min of NMES over the common peroneal nerve trunk delivered at 10, 50 and 100 Hz in a single participant. **b** Amplitude of MEPs recorded from TA averaged across the group ($n = 8$) before (pre), during (2–40 min), and after (post) NMES at each frequency. *Open triangles* signify a significant difference from pre while *asterisks* indicate a significant difference between NMES at 100 Hz and both NMES at 10 and 50 Hz (adapted from Mang et al. 2010)

on separate days in the same group of participants. The FES was delivered at 100 Hz as described in the previous paragraph and the SS was delivered at 10 Hz in a 500 ms on–500 ms off pattern at motor threshold for 2 h, as has been used previously to increase CS excitability for the hand (Ridding et al. 2000). We hypothesised that the FES would increase CS excitability more than the SS due to the greater sensory volley generated, both in terms of number of sensory axons stimulated (pulse amplitude), impulses per second (pulse frequency) and absolute number of stimuli delivered. Both protocols increased CS excitability, as can be seen in the data from a single participant in Fig. 8a. Across the group of 15 participants, a repeated measures analysis of variance identified a significant effect of time (before versus after the NMES session) on MEP amplitude, but no effect of protocol (FES vs. SS) and no interaction; these results are shown in Fig. 8b. Thus, cortical excitability increased significantly (by ~30%) after both protocols, but the magnitude of the increase was not different between these two very different forms of NMES. The lack of a difference between the two may be due to a ceiling effect in the extent to which NMES can increase CS excitability. Clearly, there will be a limit to how much NMES can increase cortical excitability and these data suggest that both the FES and SS may have been effective at reaching this ceiling. Further support for this idea comes from experiments showing that increases in CS excitability

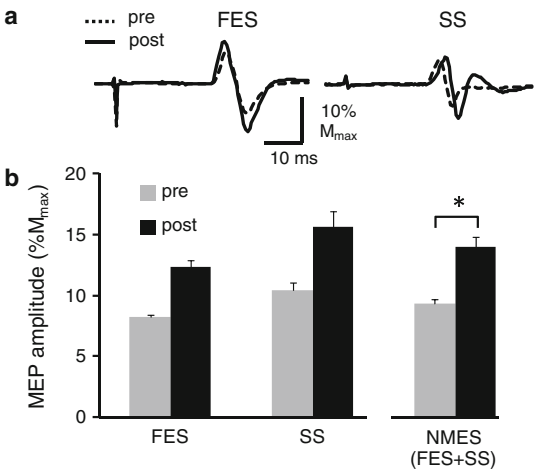

Fig. 8 **a** Changes in MEP amplitude in abductor pollicis brevis following FES and SS protocols in a single participant. Mean MEP waveforms ($n = 10$) before (pre) and after (post) stimulation of the median nerve trunk at the wrist are shown. **b** MEP amplitude before (pre) and after (post) FES and SS averaged across the group ($n = 15$). The *bars* labelled *NMES* (*FES* + *SS*) represent the data collapsed across NMES protocols and the *asterisk* shows the significant main effect of time. *Error bars* represent one standard error (Mang, Clair and Collins, unpublished data)

reach a plateau and do not increase further after 24 min of FES (see Fig. 7b; Mang et al. 2010) and after 45 min of SS (McKay et al. 2002a). Whether these two forms of NMES

increase CS excitability at the same rate or whether the excitability remains elevated for the same length of time has not been explored.

NMES and cortical circuits: differences between the arms and legs

As mentioned previously, NMES parameters that have been used to increase cortical excitability for muscles of the leg (FES) have been very different from those used for muscles of the hand (SS). Thus, although making a comparison of the effect of NMES on CS excitability for muscles of the leg and hand has been difficult, the available evidence suggests that the effect may be different for muscles in the upper and lower limbs. Following stimulation of the ulnar nerve trunk in the arm, MEPs evoked in ulnar-innervated muscles, aductor digiti minimi and first dorsal interosseous in the hand, increased by ~50%, whereas MEPs evoked in muscles not innervated by the ulnar nerve did not change (Ridding et al. 2000). Likewise, when NMES was applied to activate afferents from the first dorsal interosseous, there were increases in MEPs for first dorsal interosseous and no change in MEPs in abductor pollicis brevis (Ridding et al. 2001). These two studies and others (McKay et al. 2002a; Pitcher et al. 2003) suggest that changes in the excitability of cortical projections to hand muscles are specific to the muscles innervated by stimulated nerve and do not spread to other muscles. Whether a similar specificity occurs for muscles of the leg has been less clear. Following NMES to activate TA, MEPs recorded from TA increased while MEPs in the antagonist muscle, soleus, did not change (Khaslavskaia et al. 2002; Knash et al. 2003). In another study, common peroneal nerve stimulation was applied to activate TA during the swing phase of locomotion and MEPs increased for both TA and the antagonist muscle, soleus, suggesting that changes in CS excitability may spread to non-stimulated muscles of the leg (Kido and Stein 2004). However, the increases in soleus MEPs were more variable than those observed for TA and may have been due to the activity associated with locomotion and not the NMES. Whether these apparent differences in the way NMES affects CS excitability between the hand and the leg are due to physiological differences in CNS circuits controlling the upper and lower limbs or are simply due to the different protocols used in the studies performed on different limbs has not been clear.

Therefore, to compare the specificity of the effect of NMES between the leg and hand we investigated NMES-induced changes in CS excitability in target (i.e. innervated

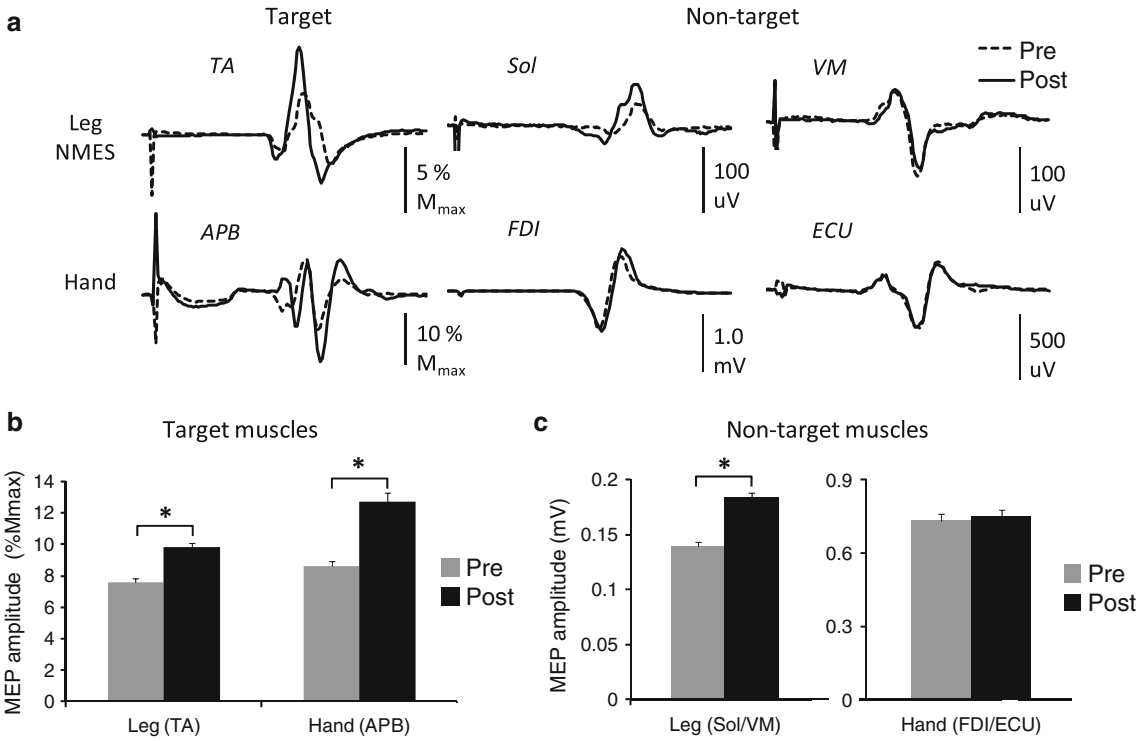

Fig. 9 **a** MEP amplitude changes in the target (*TA* tibialis anterior, *APB* abductor pollicis brevis) and non-target (*Sol* soleus, *FDI* first dorsal interosseous, *VM* vastus medialis, *ECU* extensor carpi ulnaris) muscles for FES of the median nerve trunk at the wrist and common peroneal nerve trunk at the head of the fibula to evoke an M-wave of 5% M_{max} in the target muscle. MEP amplitude before (pre) and after (post) FES averaged across the group ($n = 10$) for target (**b**) and non-target (**c**) muscles of the hand and leg. *Asterisks* show significant main effect of time. *Error bars* represent one standard error (adapted from Mang et al. 2011)

by the stimulated nerve) and non-target (i.e. not innervated by the stimulated nerve) muscles of the hand and leg in the same participants by measuring MEPs before and after a 40-min session of FES (Mang et al. 2011). As shown in Fig. 9, CS excitability increased in the target muscle in both the arm and the leg. For the leg, but not the hand, CS excitability increased in non-target muscles. This difference in the effect of NMES on CS excitability for muscles of the leg and hand is consistent with studies investigating the sensory-conditioning of MEPs by a preceding electrical stimulus to a sensory nerve and together these studies suggest that CS excitability is affected differently by sensory input received from the hand and leg (Kasai et al. 1992; Nielsen et al. 1992; Roy and Gorassini 2008). Thus, when NMES is applied to increase CS excitability for muscles in the hand, the effect is specific to the muscle being stimulated, but when NMES is applied over leg muscles, beneficial effects on CNS circuits can occur for muscles throughout the limb.

Summary

NMES activates both motor and sensory axons under the stimulating electrodes. The activation of motor axons generates contractions through *peripheral* pathways and can produce functional movements and improve muscle quality for training or rehabilitation. The activation of sensory axons can also generate contractions, by signals travelling along *central* pathways. Transmission along *central* pathways generates contraction by the synaptic activation of motor units in the spinal cord, thereby utilising mechanisms employed during voluntary contractions that cannot contribute when contractions are produced through *peripheral* pathways. The extent to which *central* pathways contribute to electrically evoked contractions depends on parameters of the stimulation, the muscle stimulated and the location at which the stimulation is delivered (i.e. over the nerve trunk or muscle belly). In general, regardless of NMES location, to generate contractions with a significant *central* contribution requires that the stimulation be delivered at low pulse amplitudes (to minimize antidromic block), long pulse durations (to increase the activation of sensory axons), and high pulse frequencies (to increase the rate at which the sensory volley is sent to the CNS). Contractions generated by NMES over a nerve trunk, but not a muscle belly, also have a significant *central* contribution, through H-reflexes, even when the stimulation is delivered at relatively low frequencies. Motor unit recruitment through *central* pathways may be more orderly, less synchronous and more spatially diffuse throughout the muscle, than recruitment through purely *peripheral* pathways. Accordingly, enhancing *central* recruitment during NMES may lead to contractions that are more fatigue resistant and may improve the way NMES can maintain muscle quality after injury or disease, although these ideas require further investigation.

The electrically evoked sensory volley also traverses the CNS and this can lead to short- and long-term plasticity in circuits that control movement. Utilising the sensory volley to evoke enduring changes in transmission through spinal circuits may be one way to reverse the maladaptive plasticity that develops in these circuits after an injury or disease. Such maladaptive plasticity includes the development of stretch reflex hyper-excitability and reduced agonist–antagonist reciprocal inhibition, both of which are thought to underlie the development of spasticity (Field-Fote 2004). Further research is required to identify the best way to deliver NMES to induce such changes. The electrically evoked sensory volley also traverses the brain, increasing activity in CS circuits, strengthening CS pathways and improving neuromuscular function. The myriad combinations of NMES parameters used to promote plasticity in CS pathways has made the identification of optimal protocols difficult, although delivering NMES at 100 Hz may be optimal for increasing CS excitability, at least for the TA muscle. Whether the effect of NMES on CS excitability is different for different muscles is not clear, however, there do seem to be differences between muscles of the upper and lower limbs. NMES can have a global effect on CS excitability for muscles of the leg, whereby excitability increases in both target and non-target muscles. In contrast, NMES of hand muscles has a more focused effect, and CS excitability increases only for muscles innervated by the stimulated nerve (i.e. target muscles). In summary, optimising the sensory volley generated during NMES to take advantage of mechanisms inherent to the neuromuscular system, such as Henneman's size principle and neuromuscular plasticity, may help to maximize the potential of NMES therapies for rehabilitation and enhance neuromuscular function at the level of the muscle, spinal cord and brain after injury or disease of the CNS.

References

Adams GR, Harris RT, Woodard D, Dudley GA (1993) Mapping of electrical muscle stimulation using MRI. J Appl Physiol 74:532–537

Adrian ED, Bronk DW (1929) The discharge of impulses in motor nerve fibres: Part II. The frequency of discharge in reflex and voluntary contractions. J Physiol 67:i3–i151

Baker LL, Wederich CL, McNeal DR, Newsam CJ, Waters RL (2000) Neuromuscular electrical stimulation: a pratical guide. Los Amigos Research and Educational Institute, Downey

Baldwin ER, Klakowicz PM, Collins DF (2006) Wide-pulse-width, high-frequency neuromuscular stimulation: implications for functional electrical stimulation. J Appl Physiol 101:228–240

Bawa P, Pang MY, Olesen KA, Calancie B (2006) Rotation of motoneurons during prolonged isometric contractions in humans. J Neurophysiol 96:1135–1140

Bergquist AJ, Clair JM, Collins DF (2011) Motor unit recruitment when neuromuscular electrical stimulation is applied over a nerve trunk compared to a muscle belly: triceps surae. J Appl Physiol 110:627–637

Bigland-Ritchie B, Zijdewind I, Thomas CK (2000) Muscle fatigue induced by stimulation with and without doublets. Muscle Nerve 23:1348–1355

Binder-Macleod SA, Clamann HP (1989) Force output of cat motor units stimulated with trains of linearly varying frequency. J Neurophysiol 61:208–217

Binder-Macleod SA, Scott WB (2001) Comparison of fatigue produced by various electrical stimulation trains. Acta Physiol Scand 172:195–203

Blair EA, Erlanger J (1933) A comparison of the characteristics of axons through their individual electrical responses. Am J Physiol 106:524–564

Blickenstorfer A, Kleiser R, Keller T, Keisker B, Meyer M, Riener R, Kollias S (2008) Cortical and subcortical correlates of functional electrical stimulation of wrist extensor and flexor muscles revealed by fMRI. Hum Brain Mapp 3:963–975

Blouin JS, Walsh LD, Nickolls P, Gandevia SC (2009) High-frequency submaximal stimulation over muscle evokes centrally generated forces in human upper limb skeletal muscles. J Appl Physiol 106:370–377

Boerio D, Jubeau M, Zory R, Maffiuletti NA (2005) Central and peripheral fatigue after electrostimulation-induced resistance exercise. Med Sci Sports Exerc 37:973–978

Buchthal F, Schmalbruch H (1970) Contraction times of twitches evoked by H-reflexes. Acta Physiol Scand 80:378–382

Burke D, Schiller HH (1976) Discharge pattern of single motor units in the tonic vibration reflex of human triceps surae. J Neurol Neurosurg Psychiatry 39:729–741

Burke D, Gandevia SC, McKeon B (1983) The afferent volleys responsible for spinal proprioceptive reflexes in man. J Physiol 339:535–552

Burke D, Kiernan MC, Bostock H (2001) Excitability of human axons. Clin Neurophysiol 112:1575–1585

Burnham R, Martin T, Stein R, Bell G, MacLean I, Steadward R (1997) Skeletal muscle fibre type transformation following spinal cord injury. Spinal Cord 35:86–91

Clair JM, Anderson-Reid JM, Graham CM, Collins DF (2011) Post-activation depression and recovery of reflex transmission during repetitive electrical stimulation of the human tibial nerve. J Neurophysiol [Epub ahead of Print]

Classen J, Liepert J, Wise SP, Hallett M, Cohen LG (1998) Rapid plasticity of human cortical movement representation induced by practice. J Neurophysiol 79:1117–1123

Collins DF (2007) Central contributions to contractions evoked by tetanic neuromuscular electrical stimulation. Exerc Sport Sci Rev 35:102–109

Collins DF, Burke D, Gandevia SC (2001) Large involuntary forces consistent with plateau-like behavior of human motoneurons. J Neurosci 21:4059–4065

Collins DF, Burke D, Gandevia SC (2002a) Sustained contractions produced by plateau-like behaviour in human motoneurones. J Physiol 538:289–301

Collins DF, Gorassini M, Bennett D, Burke D, Gandevia SC (2002b) Recent evidence for plateau potentials in human motoneurones. Adv Exp Med Biol 508:227–235

Conforto AB, Kaelin-Lang A, Cohen LG (2002) Increase in hand muscle strength of stroke patients after somatosensory stimulation. Ann Neurol 51:122–125

Crone C, Nielsen J (1989) Methodological implications of the post activation depression of the soleus H-reflex in man. Exp Brain Res 78:28–32

Crone C, Nielsen J, Petersen N, Ballegaard M, Hultborn H (1994) Disynaptic reciprocal inhibition of ankle extensors in spastic patients. Brain 117(Pt 5):1161–1168

Dean JC, Yates LM, Collins DF (2007) Turning on the central contribution to contractions evoked by neuromuscular electrical stimulation. J Appl Physiol 1:170–176

Deuchert M, Ruben J, Schwiemann J, Meyer R, Thees S, Krause T, Blankenburg F, Villringer K, Kurth R, Curio G, Villringer A (2002) Event-related fMRI of the somatosensory system using electrical finger stimulation. NeuroReport 13:365–369

Doherty TJ, Brown WF (1993) The estimated numbers and relative sizes of thenar motor units as selected by multiple point stimulation in young and older adults. Muscle Nerve 16:355–366

Dudley-Javoroski S, Shields RK (2008) Muscle and bone plasticity after spinal cord injury: review of adaptations to disuse and to electrical muscle stimulation. J Rehabil Res Dev 45:283–296

Everaert DG, Thompson AK, Chong SL, Stein RB (2010) Does functional electrical stimulation for foot drop strengthen corticospinal connections? Neurorehabil Neural Repair 24:168–177

Feiereisen P, Duchateau J, Hainaut K (1997) Motor unit recruitment order during voluntary and electrically induced contractions in the tibialis anterior. Exp Brain Res 114:117–123

Field-Fote EC (2004) Electrical stimulation modifies spinal and cortical neural circuitry. Exerc Sport Sci Rev 32:155–160

Fraser C, Power M, Hamdy S, Rothwell J, Hobday D, Hollander I, Tyrell P, Hobson A, Williams S, Thompson D (2002) Driving plasticity in human adult motor cortex is associated with improved motor function after brain injury. Neuron 34:831–840

Frigon A, Thompson CK, Johnson MD, Manuel M, Hornby TG, Heckman CJ (2011) Extra forces evoked during electrical stimulation of the muscle or its nerve are generated and modulated by a length-dependent intrinsic property of muscle in humans and cats. J Neurosci 31:5579–5588

Gondin J, Giannesini B, Vilmen C, Dalmasso C, le Fur Y, Cozzone PJ, Bendahan D (2010) Effects of stimulation frequency and pulse duration on fatigue and metabolic cost during a single bout of neuromuscular electrical stimulation. Muscle Nerve 41:667–678

Gondin J, Brocca L, Bellinzona E, D'Antona G, Maffiuletti NA, Miotti D, Pellegrino MA, Bottinelli R (2011) Neuromuscular electrical stimulation training induces atypical adaptations of the human skeletal muscle phenotype: a functional and proteomic analysis. J Appl Physiol 110:433–450

Gorman PH, Mortimer JT (1983) The effect of stimulus parameters on the recruitment characteristics of direct nerve stimulation. IEEE Trans Biomed Eng 30:407–414

Gottlieb GL, Agarwal GC (1976) Extinction of the Hoffmann reflex by antidromic conduction. Electroencephalogr Clin Neurophysiol 41:19–24

Gregory CM, Bickel CS (2005) Recruitment patterns in human skeletal muscle during electrical stimulation. Phys Ther 85:358–364

Gregory CM, Dixon W, Bickel CS (2007) Impact of varying pulse frequency and duration on muscle torque production and fatigue. Muscle Nerve 35:504–509

Grill WM, Mortimer JT (1996) The effect of stimulus pulse duration on selectivity of neural stimulation. IEEE Trans Biomed Eng 43:161–166

Hagbarth KE, Eklund G (1966) Tonic vibration reflexes (TVR) in spasticity. Brain Res 2:201–203

Hamdy S, Rothwell JC, Aziz Q, Singh KD, Thompson DG (1998) Long-term reorganization of human motor cortex driven by short-term sensory stimulation. Nat Neurosci 1:64–68

Henneman E (1957) Relation between size of neurons and their susceptibility to discharge. Science 126:1345–1347
Hoffman LR, Field-Fote EC (2007) Cortical reorganization following bimanual training and somatosensory stimulation in cervical spinal cord injury: a case report. Phys Ther 87:208–223
Hortobagyi T, Scott K, Lambert J, Hamilton G, Tracy J (1999) Cross-education of muscle strength is greater with stimulated than voluntary contractions. Mot Control 3:205–219
Hugon M (1973) Methodology of the Hoffmann Reflex in Man. New Dev Electromyogr Clin Neurophysiol 3:277–293
Jacobs PL, Nash MS (2004) Exercise recommendations for individuals with spinal cord injury. Sports Med 34:727–751
Jubeau M, Gondin J, Martin A, Sartorio A, Maffiuletti NA (2007) Random motor unit activation by electrostimulation. Int J Sports Med 28:901–904
Jusic A, Baraba R, Bogunovic A (1995) H-reflex and F-wave potentials in leg and arm muscles. Electromyogr Clin Neurophysiol 35:471–478
Kasai T, Kawanishi M, Yahagi S (1992) The effects of wrist muscle vibration on human voluntary elbow flexion-extension movements. Exp Brain Res 90:217–220
Kesar T, Chou LW, Binder-Macleod SA (2007) Effects of stimulation frequency versus pulse duration modulation on muscle fatigue. J Electromyogr Kinesiol 4:662–671
Khaslavskaia S, Ladouceur M, Sinkjaer T (2002) Increase in tibialis anterior motor cortex excitability following repetitive electrical stimulation of the common peroneal nerve. Exp Brain Res 145:309–315
Kido TA, Stein RB (2004) Short-term effects of functional electrical stimulation on motor-evoked potentials in ankle flexor and extensor muscles. Exp Brain Res 159:491–500
Kiernan MC, Mogyoros I, Burke D (1996) Differences in the recovery of excitability in sensory and motor axons of human median nerve. Brain 119:1099–1105
Kim CK, Bangsbo J, Strange S, Karpakka J, Saltin B (1995) Metabolic response and muscle glycogen depletion pattern during prolonged electrically induced dynamic exercise in man. Scand J Rehabil Med 27:51–58
Klakowicz PM, Baldwin ER, Collins DF (2006) Contribution of m-waves and h-reflexes to contractions evoked by tetanic nerve stimulation in humans. J Neurophysiol 96:1293–1302
Knaflitz M, Merletti R, de Luca CJ (1990) Inference of motor unit recruitment order in voluntary and electrically elicited contractions. J Appl Physiol 68:1657–1667
Knash ME, Kido A, Gorassini M, Chan KM, Stein RB (2003) Electrical stimulation of the human common peroneal nerve elicits lasting facilitation of cortical motor-evoked potentials. Exp Brain Res 153:366–377
Knight CA, Kamen G (2005) Superficial motor units are larger than deeper motor units in human vastus lateralis muscle. Muscle Nerve 31:475–480
Lagerquist O, Collins DF (2008) Stimulus pulse-width influences H-reflex recruitment but not H(max)/M(max) ratio. Muscle Nerve 37:483–489
Lagerquist O, Collins DF (2010) Influence of stimulus pulse width on M-waves, H-reflexes, and torque during tetanic low-intensity neuromuscular stimulation. Muscle Nerve 42:886–893
Lagerquist O, Walsh LD, Blouin JS, Collins DF, Gandevia SC (2009) Effect of a peripheral nerve block on torque produced by repetitive electrical stimulation. J Appl Physiol 107:161–167
Lang AH, Vallbo ÅB (1967) Motoneuron activation by low intensity tetanic stimulation of muscle afferents in man. Exp Neurol 18:383–391
Lexell J, Henriksson-Larsen K, Sjostrom M (1983) Distribution of different fibre types in human skeletal muscles. 2. A study of cross-sections of whole m. vastus lateralis. Acta Physiol Scand 117:115–122
Liberson WT, Holmquest HJ, Scot D, Dow M (1961) Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. Arch Phys Med Rehabil 42:101–105
Liepert J, Bauder H, Wolfgang HR, Miltner WH, Taub E, Weiller C (2000) Treatment-induced cortical reorganization after stroke in humans. Stroke 31:1210–1216
Maffiuletti NA (2010) Physiological and methodological considerations for the use of neuromuscular electrical stimulation. Eur J Appl Physiol 110:223–234
Maffiuletti NA, Zory R, Miotti D, Pellegrino MA, Jubeau M, Bottinellu R (2006) Neuromuscular adaptations to electrostimulation resistance training. Am J Phys Med Rehabil 85:167–175
Magalhaes FH, Kohn AF (2010) Vibration-induced extra torque during electrically-evoked contractions of the human calf muscles. J Neuroeng Rehabil 7:26
Major LA, Jones KE (2005) Simulations of motor unit number estimation techniques. J Neural Eng 2:17–34
Mang CS, Lagerquist O, Collins DF (2010) Changes in corticospinal excitability evoked by common peroneal nerve stimulation depend on stimulation frequency. Exp Brain Res 203:11–20
Mang CS, Clair JM, Collins DF (2011) Neuromuscular electrical stimulation has a global effect on corticospinal excitability for leg muscles and a focused effect for hand muscles. Exp Brain Res 209:355–363
McKay D, Brooker R, Giacomin P, Ridding M, Miles T (2002a) Time course of induction of increased human motor cortex excitability by nerve stimulation. NeuroReport 13:1271–1273
McKay DR, Ridding MC, Thompson PD, Miles TS (2002b) Induction of persistent changes in the organisation of the human motor cortex. Exp Brain Res 143:342–349
Mesin L, Merlo E, Merletti R, Orizio C (2010) Investigation of motor unit recruitment during stimulated contractions of tibialis anterior muscle. J Electromyogr Kinesiol 20:580–589
Milner-Brown HS, Stein RB, Yemm R (1973) The orderly recruitment of human motor units during voluntary isometric contractions. J Physiol 230:359–370
Mogyoros I, Kiernan MC, Burke D (1996) Strength-duration properties of human peripheral nerve. Brain 119:439–447
Nielsen J, Kagamihara Y, Crone C, Hultborn H (1992) Central facilitation of Ia inhibition during tonic ankle dorsiflexion revealed after blockade of peripheral feedback. Exp Brain Res 88:651–656
Panizza M, Nilsson J, Hallett M (1989) Optimal stimulus duration for the H reflex. Muscle Nerve 12:576–579
Panizza M, Nilsson J, Roth BJ, Basser PJ, Hallett M (1992) Relevance of stimulus duration for activation of motor and sensory fibers: implications for the study of H-reflexes and magnetic stimulation. Electroencephalogr Clin Neurophysiol 85:22–29
Perez MA, Field-Fote EC, Floeter MK (2003) Patterned sensory stimulation induces plasticity in reciprocal Ia inhibition in humans. J Neurosci 23:2014–2018
Pierrot-Deseilligny E, Mazevet D (2000) The monosynaptic reflex: a tool to investigate motor control in humans. Interest and limits. Neurophysiol Clin 30:67–80
Pitcher JB, Ridding MC, Miles TS (2003) Frequency-dependent, bi-directional plasticity in motor cortex of human adults. Clin Neurophysiol 114:1265–1271
Place N, Casartelli N, Glatthorn JF, Maffiuletti NA (2010) Comparison of quadriceps inactivation between nerve and muscle stimulation. Muscle Nerve 42:894–900
Ridding MC, Brouwer B, Miles TS, Pitcher JB, Thompson PD (2000) Changes in muscle responses to stimulation of the motor cortex

induced by peripheral nerve stimulation in human subjects. Exp Brain Res 131:135–143

Ridding MC, McKay DR, Thompson PD, Miles TS (2001) Changes in corticomotor representations induced by prolonged peripheral nerve stimulation in humans. Clin Neurophysiol 112:1461–1469

Round JM, Barr FM, Moffat B, Jones DA (1993) Fibre areas and histochemical fibre types in the quadriceps muscle of paraplegic subjects. J Neurol Sci 116:207–211

Roy FD, Gorassini MA (2008) Peripheral sensory activation of cortical circuits in the leg motor cortex of man. J Physiol 17:4091–4105

Schindler-Ivens S, Shields RK (2000) Low frequency depression of H-reflexes in humans with acute and chronic spinal-cord injury. Exp Brain Res 133:233–241

Selkowitz DM (1985) Improvement in isometric strength of the quadriceps femoris muscle after training with electrical stimulation. Phys Ther 65:186–196

Sheffler LR, Chae J (2007) Neuromuscular electrical stimulation in neurorehabilitation. Muscle Nerve 35:562–590

Shields RK (1995) Fatigability, relaxation properties, and electromyographic responses of the human paralyzed soleus muscle. J Neurophysiol 73:2195–2206

Shields RK (2002) Muscular, skeletal, and neural adaptations following spinal cord injury. J Orthop Sports Phys Ther 32:65–74

Solomonow M (1984) External control of the neuromuscular system. IEEE Trans Biomed Eng 31:752–763

Spiegel J, Tintera J, Gawehn J, Stoeter P, Treede RD (1999) Functional MRI of human primary somatosensory and motor cortex during median nerve stimulation. Clin Neurophysiol 110:47–52

Stein RB, Gordon T, Jefferson J, Sharfenberger A, Yang JF, de Zepetnek JT, Belanger M (1992) Optimal stimulation of paralyzed muscle after human spinal cord injury. J Appl Physiol 72:1393–1400

Stein RB, Everaert DG, Thompson AK, Chong SL, Whittaker M, Robertson J, Kuether G (2010) Long-term therapeutic and orthotic effects of a foot drop stimulator on walking performance in progressive and nonprogressive neurological disorders. Neurorehabil Neural Repair 24:152–167

Stevens JE, Mizner RL, Snyder-Mackler L (2004) Neuromuscular electrical stimulation for quadriceps muscle strengthening after bilateral total knee arthroplasty: a case series. J Ortho Sports Phys Ther 34:21–29

Stotz PJ, Bawa P (2001) Motor unit recruitment during lengthening contractions of human wrist flexors. Muscle Nerve 24:1535–1541

Theurel J, Lepers R, Pardon L, Maffiuletti NA (2007) Differences in cardiorespiratory and neuromuscular responses between voluntary and stimulated contractions of the quadriceps femoris muscle. Respir Physiol Neurobiol 157:341–347

Thomas CK, Nelson G, Than L, Zijdewind I (2002) Motor unit activation order during electrically evoked contractions of paralyzed or partially paralyzed muscles. Muscle Nerve 25:797–804

Thompson AK, Estabrooks KL, Chong S, Stein RB (2009) Spinal reflexes in ankle flexor and extensor muscles after chronic central nervous system lesions and functional electrical stimulation. Neurorehabil Neural Repair 23:133–142

Trimble MH, Enoka RM (1991) Mechanisms underlying the training effects associated with neuromuscular electrical stimulation. Phys Ther 71:273–280

van Boxtel A (1986) Differential effects of low-frequency depression, vibration-induced inhibition, and posttetanic potentiation on H-reflexes and tendon jerks in the human soleus muscle. J Neurophysiol 55:551–568

Vanderthommen M, Depresseux JC, Dauchat L, Degueldre C, Croisier JL, Crielaard JM (2000) Spatial distribution of blood flow in electrically stimulated human muscle: a positron emission tomography study. Muscle Nerve 23:482–489

Vanderthommen M, Duteil S, Wary C, Raynaud JS, Leroy-Willig A, Crielaard JM, Carlier PG (2003) A comparision of voluntary and electrically induced contractions by interleaved 1H- and 31P-NMRS in humans. J Appl Physiol 94:1012–1024

Veale JL, Mark RF, Rees S (1973) Differential sensitivity of motor and sensory fibres in human ulnar nerve. J Neurol Neurosurg Psychiatry 36:75–86