Comparing the Effects of Functional Electrical Stimulation Versus Somatosensory Stimulation on Increasing Corticospinal Excitability for a Muscle of the Hand

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Abstract: The electrically-evoked afferent volley generated during NeuroMuscular Electrical Stimulation (NMES) can increase the excitability of CorticoSpinal (CS) pathways. Over time, NMES can strengthen damaged CS pathways and result in enduring improvements in function for persons with central nervous system injury or disease. NMES-induced increases in CS excitability have been studied using a variety of NMES parameters, yet the influence of these stimulation parameters on increasing CS excitability is not well understood. NMES is commonly delivered at intensities sufficient to generate repeated functional contractions for relatively short durations (30-40 min) or at low intensities, near motor threshold, for long durations (2 h). For the purpose of this study, these different stimulation protocols are termed Functional Electrical Stimulation (FES) and Somatosensory Stimulation (SS), respectively. A direct comparison of increases in CS excitability induced by such protocols has not been conducted. Thus, the present experiments were designed to compare changes in CS excitability for Abductor Pollicis Brevis (APB) in the hand following FES and SS of the median nerve. We hypothesized that due to the generation of a larger afferent volley, the FES would increase CS excitability more than the SS. Ten Motor Evoked Potentials (MEPs) were evoked in APB using transcranial magnetic stimulation before and after each type of NMES. MEP amplitude increased significantly following both the FES (by 66 ± 7%, mean ± standard error) and SS (49 ± 6%), but the amplitude of these increases was not significantly different. These results suggest that just 40 min of FES can increase CS excitability, and potentially provide rehabilitative benefits, to the same extent as 2 h of SS.

Keywords: physiotherapy; kinesiology; neurophysiology; neurorehabilitation

1. Introduction

Enduring improvements in motor function following NeuroMuscular Electrical Stimulation (NMES) are associated with increased excitability of CorticoSpinal (CS) pathways (Knash et al. 2003; Everaert et al. 2010). Such increases in CS excitability are driven by the
electrically-evoked afferent volley and have been shown when using a variety of combinations of stimulation parameters (intensity, frequency, pulse width, duty cycle, and duration) (Chipchase et al. 2011a). A systematic review examining the effect of NMES parameters on induction of cortical plasticity concluded that increasing stimulation intensity enhances NMES effects, but that further studies are needed before definitive conclusions can be made about the effects of altering other NMES parameters (Chipchase et al. 2011a). Across studies examining NMES effects on CS excitability, stimulation intensities have varied from below motor threshold (Hoffman and Field-Fote 2007) to 50% of a maximal motor wave (M_{max}) (Kido and Stein 2004). M_{max} is elicited by peripheral electrical stimulation and reflects the maximal motor fibre recruitment in the activated muscle (Calder et al. 2005). Frequencies have also varied from 3 Hz (Pitcher et al. 2003) to 200 Hz (Khaslavskaya et al. 2002), and pulse durations have ranged from 200 μs (Fraser et al. 2002) to 1 ms (Knash et al. 2003) across studies. In addition, NMES has been applied in a variety of different duty cycles (500 ms on, 500 ms off to 20 s on, 20 s off) (Ridding et al. 2000; Mang et al. 2010) and for differing durations (10 min to 2 h) (Fraser et al. 2011; Ridding et al. 2000). Despite the wide range of parameters used in different studies (Chipchase et al. 2011a), comparisons of the effects of varying stimulation parameters have rarely been conducted, and thus, the influence of these parameters on increasing CS excitability for muscles of the hand is not well defined.

The present experiments are the first designed to compare the effects of two commonly utilized NMES protocols on CS excitability for a muscle of the hand. NMES was applied to the median nerve at the wrist to increase CS excitability for the Abductor Pollicis Brevis (APB) muscle. The median nerve was chosen because it has been studied previously (Conforto et al. 2002; Hoffman and Field-Fote 2007) and is stimulated for rehabilitation of grasping (Sheffler and Chae 2007). One stimulation protocol that we tested was a Functional Electrical Stimulation (FES) protocol that we have used previously to increase CS excitability for muscles in the leg and hand (Mang et al. 2010, Mang et al. 2011). FES is a type of NMES that is generally characterized by its relatively high stimulation intensities that produce muscle contractions to generate functional movements (i.e. grasping, walking) for relatively short periods of time (~30-40 min). The FES protocol we employed in this study consisted of a relatively high frequency (100 Hz) and a wide pulse width (1 ms) delivered in a 20 s on, 20 s off pattern for 40 min at an intensity sufficient to generate an M-wave that was 15% of M_{max}. We chose these parameters based on previous work indicating that high frequency (100 Hz) and wide pulse
width (1 ms) stimulation enhances the sensory volley transmitted to the Central Nervous System (CNS) by NMES compared to lower frequency and narrower pulse width NMES (Baldwin et al. 2006). The 20 s on, 20 s off duty cycle and intensity of 15% $M_{\text{max}}$ were chosen to elicit a functional contraction in terms of duration and amplitude, and the 40 min duration was chosen based on previous work showing it is a sufficient duration to evoke increases in CS excitability (Mang et al. 2010, 2011). The other stimulation protocol was a Somatosensory Stimulation (SS) protocol that is commonly used to increase CS excitability in hand muscles. Generally, SS is characterized by its low stimulation intensities (near motor threshold) and long durations (~2 h). SS is designed to primarily activate sensory axons and prime CNS circuits to increase CS excitability for rehabilitation sessions without producing large or functional muscle contractions (Hoffman and Field-Fote 2007). The SS protocol utilized in the present study was chosen to be the same as that used in previous studies (Conforto et al. 2002; Ridding et al. 2000, 2001) and consisted of a stimulation frequency of 10 Hz and a wide pulse width (1 ms) delivered in a 0.5 s on, 0.5 s off pattern for 2 h at an intensity just high enough to elicit a visible twitch (~3-5% $M_{\text{max}}$). As FES generates a larger afferent volley (higher intensity and frequency) than SS, we hypothesized that the FES protocol would increase the amplitude of Motor Evoked Potentials (MEPs) evoked by Transcranial Magnetic Stimulation (TMS) in the stimulated muscle more than the SS protocol. The results of this study provide information that may provide guidance when selecting NMES parameters to increase CS excitability for rehabilitation of impaired grasping following CNS injury. A portion of this data was briefly discussed and presented in a previously published review article (Bergquist et al. 2011).

2. Methods

Eleven men and 4 women ranging in age from 19 to 47 years old with no known neurological disorders participated in this study. All participants gave written, informed consent prior to testing. The experimental procedures were approved by the Human Research Ethics Board at the University of Alberta. All subjects participated in 2 separate ~3 h testing sessions at least 48 h apart in which NMES was applied to the median nerve to activate APB with an FES protocol on one occasion and an SS protocol on the other. The order of testing sessions was randomized for each participant. During experimental sessions, subjects were seated with their back, neck, and right arm supported. The shoulder, elbow, and wrist angles were maintained at ~15° of flexion, 120° of flexion, and 180°, respectively. The elbow was supported by an arm support and the hand was placed on a hand
rest in a relaxed position. During the application of the FES and SS protocols, participants remained relaxed and awake. Data from 14 participants were collected during the same experimental sessions as data that were part of a companion study (Mang et al. 2011). The data that are common to the present study and the companion study are the amplitude of MEPs and $M_{\text{max}}$ values elicited during the FES session.

2.1 Electromyography (EMG)

Evoked potentials were measured with EMG recorded from APB of the right hand using bipolar surface (2.25 cm$^2$) recording electrodes (Vermed Medical, Bellows Falls, Vermont). EMG signals were pre-amplified (1,000x) and band-pass filtered at 10-1,000 Hz (NeuroLog System; Digitimer, Welwyn Garden City, Hertfordshire, England). Data were sampled at 2,000 Hz with a 12-bit A/D converter (National Instruments, Austin, Texas). During the collection of M-waves and MEPs, data were recorded in 450 ms sweeps from 100 ms before to 350 ms after stimulus delivery.

2.2 Neuromuscularelectrical stimulation (NMES)

NMES was applied over the right median nerve at the wrist using bipolar round (3.2 cm) neurostimulation electrodes (Axelgaard Manufacturing Co., Ltd.) placed at the site that evoked a response in APB (M-wave or H-reflex) at the lowest stimulation intensity. Rectangular pulses of 1 ms duration were delivered from a Digitimer (DS7A, Hertfordshire, England) constant current stimulator for all experimental sessions. Participants were instructed to remain relaxed while NMES was applied.

2.3 Functional Electrical Stimulation (FES)

The stimulation was adjusted to an intensity at which a single stimulus evoked an M-wave that was ~15% $M_{\text{max}}$ in APB. NMES was then delivered at this intensity with a stimulation frequency of 100 Hz for 40 min in a 20 s on, 20 s off cycle (see Fig. 1). A 1 ms pulse width was utilized because wide pulse NMES increases the afferent volley to the CNS and can enhance the central or “reflexive” contribution to electrically-evoked contractions (Lagerquist and Collins 2008, 2010). Likewise, a frequency of 100 Hz was utilized because we have previously shown that 100 Hz NMES increases CS excitability more than 10, 50, or 200 Hz NMES (Mang et al. 2010).

2.4 Somatosensory Stimulation (SS)

SS was applied at an intensity that evoked a small, just visible, twitch in APB (~3-5% $M_{\text{max}}$) and at a frequency of 10 Hz. The stimulation was applied for a total duration of 2 h in a 500 ms on, 500 ms off cycle (see Fig. 1).
The total number of pulses received in the SS protocol was 36,000 relative to 120,000 during the FES protocol. We were not concerned with controlling the total volume of stimulation between protocols as our primary aim was simply to compare the effects of these two previously established NMES protocols.

Figure 1. A schematic of the protocols used for FES and SS. Each grey box represents a period of NMES and is followed by a black line which represents a rest period. FES stimulation was delivered at an intensity of 15% $M_{\text{max}}$, a frequency of 100 Hz, and a pulse width of 1 ms. SS stimulation was delivered at an intensity near motor threshold, a frequency of 10 Hz, and a pulse width of 1 ms.

2.5 Transcranial magnetic stimulation (TMS)

To test the excitability of the CS pathway, MEPs were evoked using TMS (Magpro R30; Medtronic Inc., Minneapolis, Minnesota) applied with a parabolic (Medtronic MMC-140, Minneapolis, Minnesota) or figure-of-eight coil (Medtronic MC-B70, Minneapolis, Minnesota). For a given subject, the same coil was used in both sessions. All MEPs were evoked while subjects were relaxed. MEPs were evoked from the hotspot for right APB. The hotspot was found before the application of NMES by moving the coil over the left motor cortex to find the site that elicited the largest amplitude MEP in APB at the lowest intensity of stimulation. Using a Brainsight image-guided stimulation system (Rogue Research, Montreal, Quebec) the site was recorded and the coil was manually held in place to maintain position and orientation (precision: ± 3 mm) during measurement trials. Resting MEP threshold was then determined by finding the lowest intensity that produced MEPs of at least 50 uV in response to 4 out of 8 stimuli. The intensity of TMS was then set at 120% of the threshold for the measurements. Ten MEPs were evoked and recorded from APB immediately before (pre) and after (post) the prolonged period of NMES. The MEPs were evoked at an inter-stimulus interval that varied randomly between 4-6 s.

3. Maximal M-waves ($M_{\text{max}}$)

To determine $M_{\text{max}}$ for APB, stimulation intensity was varied from below motor threshold to 1.5-2 times the minimum current required to evoke $M_{\text{max}}$ over 5 stimuli. $M_{\text{max}}$ was calculated as the largest M-wave evoked in APB. The amplitude of
M_{max} was tested on 3 occasions before and 3 occasions after the delivery of NMES. Occasionally the amplitude of M_{max} was reduced following the NMES. In these instances the recording electrodes were replaced and M_{max} was re-collected. In some instances there were still small variations in M_{max}, despite replacement of the electrodes. Thus, all MEPs were normalized to the M_{max} recorded nearest in time to the collection of the MEPs.

4. Data Analyses

Changes in CS excitability induced by NMES were determined by quantifying and comparing the group averages of the 10 MEPs evoked before and after NMES. MEPs recorded from APB were measured peak-to-peak and normalized to M_{max}. To ensure all MEPs were obtained at rest, MEP data were inspected post-hoc and discarded if the EMG amplitude during the 1 s before the TMS exceeded 2 standard deviations of the average baseline signal recorded at rest before the stimulation. Of the 600 MEPs evoked from 15 subjects, 5 MEPs (<1% of the total responses) were removed from the analyses based on this criterion.

A two-way Repeated Measures Analysis of Variance (RM-ANOVA) test was used to compare NMES-evoked changes in APB MEP amplitude between the FES and SS protocols. The factors were NMES protocol (2 levels: FES and SS) and Time (2 levels: pre and post). The significance level was set at $p<0.05$. As no significant interactions were found and each main effect had only 2 levels, post-hoc analyses were not necessary. All descriptive statistics are reported as mean ± standard error.

5. Results

MEP amplitude for APB increased following both FES and SS, but the magnitudes of these increases were not different.

5.1 Single subject results

Fig. 2 shows mean MEP waveforms ($n=10$) recorded from APB from one participant before and after FES and SS. In this participant, MEPs increased by 48% after FES and by 46% after SS, although changes in MEP amplitude were not tested for statistical significance in individual participants.

![Fig. 2 Changes in MEP amplitude in APB following FES and SS in a single participant. Mean MEP waveforms ($n=10$) before (pre) and after (post) median nerve stimulation are shown.](image-url)
5.2 Group results

MEP amplitude for APB averaged across the group before (pre) and after (post) NMES was applied with FES and SS protocols are shown in Fig. 3. The RM-ANOVA revealed a main effect of Time \[F(1, 14)=4.61, p=0.049\], no main effect of NMES protocol \[F(1, 14)=0.96, p=0.34\], and no interaction \[F(1, 14)=0.1, p=0.76\]. Thus, MEPs from APB were significantly increased following both 40 min of FES (66 ± 7% increase; range: 284% increase to 64% decrease) and 2 hr of SS (49 ± 6% increase; range: 279% increase to 62% decrease), but the magnitude of these increases were not different.

Fig. 3 MEP amplitude before (pre) and after (post) FES and SS averaged across the group. The bars labeled “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.

6. Discussion

The present experiments were designed to compare the effect of FES and SS on CS excitability for a muscle of the hand. The main finding was that although FES was applied for just 40 min, compared to 2 h of SS, the NMES protocols increased CS excitability for APB to the same extent.

The afferent volley generated by NMES can increase CS excitability and the size of the volley depends on the stimulation parameters. For example, a functional magnetic resonance imaging study found a clear relationship between NMES intensity and hemodynamic activity in sensorimotor cortex, suggesting that higher intensities of NMES sent a larger afferent volley to the cortex than lower intensities (Smith et al. 2003). Similarly, Khaslavskaia and colleagues (2002) reported that higher intensity NMES increased CS excitability for a leg muscle more than lower intensity NMES in a single participant. In addition to stimulation intensity, frequency also influences increases in CS excitability. For example, CS excitability for a muscle of the hand increased following 30-Hz NMES and decreased following 3-Hz NMES (Pitcher et al. 2003). Likewise, 100-Hz NMES was more effective for increasing CS excitability than 10-, 50-, or 200-Hz NMES for a muscle of the leg (Mang et al. 2010). Another study evaluated the effects of NMES protocols applied to the biceps brachii muscle with different combinations of stimulation intensity and frequency. The main finding was that 30 minutes of ‘motor movement’ stimulation delivered at 30 Hz stimulation
at an intensity that ramped up gradually over 4 s (4 s on, 6 s off) to supinate the forearm and produce ~10° of elbow flexion was more effective than 5 other 30 minute NMES protocols with varying combinations of stimulation frequency, intensity and duty cycles that did not elicit functional movements (Chipchase et al. 2011b). The influence of duration of NMES is less studied, but one study found that both 20 and 40 minutes of ramped 30 Hz stimulation trains (6 s on, 4 s off) delivered just above motor threshold induced similar increases in CS excitability, but that 60 minutes of the NMES protocol did not induce an effect (Andrews et al. 2013). These studies suggest that higher NMES intensities and frequencies and durations of less than 60 minutes of NMES may be optimal for increasing CS excitability in hand muscles, yet many studies investigating NMES effects on CS excitability have utilized low intensities, low frequencies and long durations (i.e. SS) (Ridding et al. 2000, 2001; Mckay et al. 2002a). Previously, SS increased CS excitability by ~50-100% (Ridding et al. 2000, 2001; Mckay et al. 2002a) in hand muscles, but no studies have directly compared the effects on CS excitability induced by higher intensity and frequency NMES (i.e. FES) with the traditional SS protocol. The FES delivered in the present study generated a larger afferent volley than the SS in terms of stimulation intensity, pulses delivered per unit of time (100 Hz compared to 10 Hz), and absolute number of pulses delivered (120,000 to 36,000).

Our hypothesis that FES would increase CS excitability for a muscle of the hand more than SS was not supported. Despite the larger afferent volley generated by FES, the increases in CS excitability following FES (66%) and SS (49%) were not significantly different. Thus, FES applied for just 40 min was as effective for increasing CS excitability as SS applied for 2 h. Although there was an apparent 17% further increase in CS excitability following FES than SS, this difference was not significant, likely due to high inter-subject variability in the response to NMES following both protocols, rather than an issue of statistical power. Some participants showed robust increases in CS excitability following NMES, while others did not (range: 284% increase to 64% decrease). Past research has also shown high inter-subject variability (Kaelin-Lang et al. 2002; Mang et al. 2010), suggesting that NMES may increase CS excitability and be beneficial for rehabilitation for some individuals, but may have no effect or even be detrimental for others. Whether these individual differences depend on stimulation parameters, such that different individuals have different optimal NMES parameters for increasing CS excitability, has yet to be explored.

The lack of difference in the effect of FES and SS on CS excitability across the group suggests that there may be a “ceiling effect” in the extent to which CS
excitability can be increased by NMES. Previously, we found that FES (as applied in the present study) of the CP nerve in the leg increased CS excitability for tibialis anterior by the 24th minute of stimulation and CS excitability did not increase further over the remainder of the 40 min stimulation protocol (Mang et al. 2010). Likewise, McKay and colleagues (2002a) found that SS applied to the ulnar nerve at the wrist increased CS excitability after ~45-60 min, and did not increase CS excitability further over the remainder of the 2 h stimulation protocol. These studies suggest that a ceiling exists for the effect of NMES on CS excitability and that it was likely reached during both protocols utilized in the present study. Whether this ceiling was reached faster by one protocol than the other was not addressed presently, but the aforementioned studies suggest that the ceiling can be reached faster during FES than SS, although different muscles were tested. A single study comparing CS excitability changes in the same muscle throughout FES and SS protocols would determine which type of NMES increases CS excitability the fastest. Additionally, while it is important to understand how to apply NMES to increase CS excitability maximally in the shortest period of time, continuing to deliver NMES after CS excitability is maximally increased may result in longer lasting increases in CS excitability. Application of NMES on successive days produces increases in CS excitability that can last up to 2 days (McKay et al. 2002b) as compared to just ~1-2 h following a single session (McKay et al. 2002a). Whether single sessions of longer duration can also produce more enduring increases in CS excitability is not known.

In addition to stimulation parameters, NMES-induced increases in CS excitability may also depend on the number of pulses delivered. In the present study, the 40 min FES protocol consisted of a total of 120,000 pulses compared to 36,000 in the 2 h SS protocol. As SS delivered at 10 Hz has been shown to increase CS excitability in ~45-60 min (McKay et al. 2002a), this suggests that less than 18,000 pulses are needed to increase CS excitability. However, 18,000 pulses would have been delivered within the first 6 minutes of the FES and increases in CS excitability induced by NMES have not been reported in such short periods of time. Moreover, when using NMES for rehabilitation, determining the number of pulses needed to evoke changes in CS excitability is less important than determining which NMES parameters induce the changes to the greatest extent and the fastest.

Studies using SS protocols suggest that improvements in upper limb function following NMES coincide with increased CS excitability (Ridding et al. 2000; Conforto et al. 2002; McKay et al. 2002a, b; Pitcher et al. 2003; Hoffman and Field-Fote 2007). Moreover, enhanced CS
excitability has been associated with improvements in motor performance (Ziemann et al. 2001) and the acquisition of new motor skills (Pascual-Leone et al. 1995). If enhancing CS excitability leads to functional improvements, then a better understanding of how NMES can be applied to maximally increase CS excitability will be important for maximizing the efficacy of NMES therapies. Our data suggest that just 40 min of FES is as effective as 2 h of SS for increasing CS excitability. Thus, rehabilitative benefits associated with increased CS excitability could be realized to a similar extent after applying 40 min of FES as after 2 h of SS.

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