Full Title: Reducing muscle fatigue due to Functional Electrical Stimulation using random modulation of stimulation parameters

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Short Title: Reducing fatigue using random stimulation

Abstract

A major limitation of many functional electrical stimulation (FES) applications is that muscles tend to fatigue very rapidly. It was hypothesized that FES-induced muscle fatigue could be reduced by randomly modulating the pulse frequency, amplitude and pulse width in a range of +/- 15%. Seven subjects with spinal cord injuries participated in this study. FES was applied to quadriceps and tibialis anterior muscles using surface electrodes. Isometric force was measured, and the time for the force to drop by 3 dB (fatigue time) was compared between trials. Four different modes of FES were applied in random order: constant stimulation, randomized frequency, randomized amplitude, and randomized pulse width. There was no significant difference between the fatigue time measurements for the four modes of stimulation ($p = 0.329$). Therefore, random modulation appeared to have no effect. Based on an observed correlation between maximum force measurements and trial order, we concluded that 10 minute rest periods between trials was insufficient.

Key words: Neuroprostheses; Functional electrical stimulation (FES); pulse frequency; spinal cord injury (SCI); fatigue; isometric contraction.

Introduction

Functional electrical stimulation (FES) is a means of evoking contractions in paralyzed muscles by passing small electrical impulses through nervous tissue. It can be used to induce coordinated movements such as walking or grasping [1]. FES has been shown to improve impaired function, to slow down or stop bone and muscle deterioration, and to improve circulation in paralyzed limbs of spinal cord injury (SCI) and stroke patients [2]. However, one of the major limitations is that stimulated muscles tend to fatigue very rapidly, which limits the role of FES in applications such as standing and walking.

Although the exact cause of muscle fatigue is not known, it has been attributed mainly to failure at the synaptic junction, a decrease in transmitter release, and metabolic exhaustion of the contractile mechanism. In the context of SCI, the problem of fatigue is exacerbated by several physiological changes that result from paralysis, including hypertonia and disuse atrophy [3]. Long-term inactivity due to SCI is associated with chronic changes in muscle metabolism, blood flow, and fiber composition [4-7]. The bulk of the transformation in muscle fiber type (from slow- to fast-twitch) due to disuse atrophy occurs during the first ten months after injury. A muscle has greater fatigue resistance in acute paraplegics (less than 10 months post-injury) compared to chronic paraplegics (greater than 10 months post-injury) [8].

One reported solution to the muscle fatigue problem, and the basis for this study, is to apply stochastic modulation to the inter-pulse interval, which is equivalent to randomly modulating the pulse frequency [9]. It was reported in that the amount of time that a leg could be extended against gravity was increased by 37% when the inter-pulse interval of stimulation was varied in a range of +/- 12% (compared to constant frequency stimulation). This was a significant result, but it was limited to a single subject.

Other methods of fatigue reduction have practical limitations. Muscle conditioning is time consuming, requiring several weeks of intense training, and it can lead to a decrease in muscular strength due to the increase in slow fatiguing muscle fibers [4-7]. Doublet stimulation, although promising, has demonstrated both a positive and negative effect on the fatigue time depending on the test conditions and protocol [3,10-13]. Sequential stimulation of multiple motor points is not suitable for clinical use on humans since it is invasive, requiring insertion of multiple needle electrodes for each muscle [14]. Intermittent high frequency stimulation has been shown to result in greater contractile forces with less fatigue than intermittent low frequency stimulation in able-bodied and paraplegic subjects [15]. However, due to the extended periods of rest required between pulse trains, intermittent stimulation is limited to cyclic applications such as hybrid orthotics [16]. There remains a clear a need for practical solutions to the problem of FES-induced muscle fatigue as well as an understanding of the underlying mechanisms of fatigue.

The goal of this study was to reduce the rate of muscle fatigue by randomly modulating FES signal parameters. We hypothesized that by randomly modulating the pulse frequency, amplitude and width, the resulting firing rate and level of recruitment of motor units would vary over time. A constantly changing firing rate and recruitment level should increase and decrease the total number of motor units activated, allow some motor units on the margin of stimulation brief periods of rest, and thereby increase the fatigue resistance during isometric contractions. We proposed two mechanisms by which this may occur. Firstly, variations that exist in the threshold (intensity and duration of stimulus needed to generate an action potential in axons) among motor neurons due to their differences in size and depth could be exploited. Varying the amplitude and pulse width of stimulation could excite nerve fibers of differing size and location in the nerve bundles and cause quasi-stochastic contractions of motor units with different contractile properties. Secondly, variation in the frequency of stimulation affects the frequency of action potentials and the amount of neurotransmitter released at the synaptic gap. This could lead to variation in the number of muscle fibers recruited and the level of tetany of each fiber.

Methods

Seven SCI subjects were recruited from the inpatient and outpatient population at the Toronto Rehabilitation Institute. One subject was female and 6 were male (mean age of 31.2 ± 6.2) and their level of injury ranged from C6/C7 to T8 (see Table 1). Four of the subjects were first time FES users, while three of them had previous training ranging from three months to over one year. Two muscle groups were tested bilaterally for each subject: the tibialis anterior and the quadriceps. We were not able to induce measurable contractions for the right tibialis anterior of one subject and the right and left tibialis anterior of another subject, probably due to peripheral nerve damage. Other results were rejected if the muscle exhibited spastic contractions. Data was analyzed for an equivalent of 22 muscles.

Biphasic, bipolar, current controlled stimulation pulses were administered using a stimulator and adhesive surface electrodes (Compex Motion, Ecublens, Switzerland). A pushbutton was used to trigger the onset of electrical stimulation with a linear ramp-up time of 0.5 s. As shown in Figure 1A, a pair of 5 x 5 cm electrodes were attached over the proximal (active electrode) and distal (reference electrode) ends of the tibialis anterior muscles. A 5 x 10 cm electrode was attached to the skin of the proximal (active electrode) end of the quadriceps and a 5 x 5 cm electrode to the distal (reference electrode) end of each of the quadriceps (see Figure 1C). All tests were performed while subjects were seated in an upright position on a padded bench, as shown in Figure 2B. Participants were secured in position with waist and leg straps. Isometric joint force was measured using a strain gage based, tension/compression pancake load cell (Honeywell Sensotec, Columbus, Ohio, USA – Figure 1D) with a range of -1100 to 1100 N. The signal from the load cell was amplified using a strain gage conditioner (Daytronic Corporation, Dayton, Ohio, USA) and then passed through an analog to digital converter. Data was sampled at 1000 Hz using data acquisition software written in Labview (National Instrument Co., Austin, Texas, USA).

The load cell was mounted on the base of the apparatus in one of two positions. When knee extension moment was being measured, the load cell was mounted anterior to the subject's ankle, and a strap connected in series to the load cell was fixed to the ankle. In the second configuration, the load cell was mounted below the foot rest, and the strap was attached to the foot over the metatarsus. The load cell was thus used to measure isometric knee extension and isometric dorsiflexion moments.

Before each test, the electrodes were tested for proper placement on the muscle. Stimulus was applied with no randomization while manual resistance was applied to the joint. The pulse amplitude was increased until a level was reached where no further increase in amplitude increased the muscle force or muscle contour as perceived by the investigator. 75% of this value was used as the mean pulse amplitude for all four tests for that muscle. Four trials were performed on each muscle group; no random modulation of any parameters (control trial), random modulation of pulse amplitude (amplitude trial), random modulation of pulse frequency (frequency trial), and random modulation of pulse width (pulse width trial). A 10-minute rest time was administered between each test, which was considered to be adequate for repeatable results [3,12,13]. The order of the trials was randomized.

A mean stimulation frequency of 40 Hz was used, which has been used in previous fatigue tests [3]. A mean pulse width of 250 μs was used. The pulse amplitude was set between 34 and 110 mA, varying with each subject and muscle group and selected as described above. All three parameters when randomized were varied above and below the mean by 15% using a uniform probability distribution. Values for pulse amplitude, width, and frequency were refreshed every 100 ms.

The "fatigue time" was defined as the duration between the onset of stimulation (time zero) and the point where the force decreased to below 70% of the maximum force. Since this threshold was chosen arbitrarily, we also conducted the same analysis using thresholds of 60% and 80%. We also considered the normalized *fatigue time integral* (FTI), which is defined as follows.

$$FTI = \frac{\int_0^T F(t)dt}{F_{\max}} \tag{1}$$

where T is the fatigue time for that trial, $F(t)$ is the force over time, and F_{max} is the maximum force. In this measure, the shape of the curve is taken into account. A gradual decrease of force would yield a lower FTI value than a force that was sustained over the same period of time then dropped off suddenly.

In order to remove noise and smooth the data, a 22nd order polynomial was fitted to each curve using a least squares algorithm to facilitate data analysis (Figure 2). The order of the polynomial was determined using an iterative method on a representative sample of curves by increasing the order until the R^2-value remained the same (to 3 significant digits) for consecutive iterations. The polynomial was used to find the instant in time when the force dropped below threshold and the corresponding FTI. To approximate how much the stimulation order biased the results, the stimulation order for each muscle was compared to the order in the magnitude of maximum force, fatigue time, and FTI for each test.

The effect of the four stimulation modes was tested using an Analysis of Variance (ANOVA) for repeated measures. Separate tests were performed using fatigue time measurements and FTI measurements. We also tested the hypothesis that fatigue time and FTI were sensitive to the order of trials. Similarly, the maximum force measurements were also considered. Statistical significance was set at $P < 0.05$.

Results

Figure 3 illustrates the average values of fatigue time and FTI for all muscles using the 70% force threshold for the four modes of stimulation. Although random modulation of the amplitude, frequency and pulse width produced slightly higher fatigue time measurements than the control trials, the differences were not significantly different (p-value = 0.329). There was also no significant effect of random modulation on FTI (p-value = 0.414). Maximum Force, however, was clearly affected by the order of stimulation (p-value = 0.0029). Table 2 shows the p-values resulting from all tests for a randomization effect, an effect due to trial order, and an effect due to which leg was stimulated (left versus right).

It was confirmed by that the fatigue time and the maximum force measurements were independent. In Figure 4, all trials are plotted versus maximum force, and a best fit line was determined using least squares regression. There was very little, if any, correlation between the maximum force and the fatigue time at 70% threshold ($R^2 = 0.081$ and p-value = 0.197). Similarly, Figure 4B shows no correlation between the maximum force and the normalized FTI at 70% threshold ($R^2 = 0.047$ and p-value = 0.119).

There was no difference seen between subjects with previous FES training and subjects with no previous FES training in terms of fatigue time (p-value = 0.983) or FTI (p-value = 0.924) measurements. Further, there was no correlation between length of FES training and fatigue time ($R^2 = 0.022$, p-value =

0.073) or FTI ($R^2 = 0.016$, p-value = 0.105). In Figure 5 the average maximum force, FTI and fatigue time measurements are shown with respect to the order of the trials. The magnitude of the maximum force clearly decreases from one test to the next (Figure 5A). This, however, did not affect the normalized FTI measurements. Were the FTI measurements not normalized, they would have been highly dependent on trial order ($p < 0.0001$). The fatigue time measurements were independent of the trial order ($p = 0.229$).

Discussion

One previous study had demonstrated a significant increase in fatigue time using stochastic modulation of stimulation frequency [9]. However, it was only demonstrated on a single subject. The improved fatigue resistance could have been a result of recruiting more muscle fibers and distributing the load over more muscle or of varying the level of tetany over time of the muscle fibers. However, our results on seven different individuals showed no overall effect on fatigue of randomly modulating stimulation parameters in the range of +/- 15% about the chosen mean values.

In our experiments, a ten minute rest time was chosen due in part to time constraints and in part because repeatable results have been achieved using a ten minute rest time in previous studies [3,12,13]. In addition, studies have demonstrated a full recovery in peak force and endurance from short high intensity stimulation after only ten minutes [17] and 95% recovery in peak force from continuous maximum voluntary contractions after only three minutes [18]. Our results did not indicate a full recovery in muscles potential to reach peak force since the peak force was highly dependent on stimulation order.

Non-normalized FTI, which incorporates force, was also highly dependent on stimulation order and was therefore not a reliable measure of muscular fatigue. With a longer rest time of perhaps 30 minutes or several hours, FTI would not be influenced by previous testing and could be an effective tool for measuring fatigue. Fatigue time was not highly influenced by the order of stimulation. One possible explanation for this may be that during the first stimulation trial, the fast-twitch muscle fibers become fatigued, and then in latter trials, the contraction is caused mostly by fatigue-resistant slow-twitch fibers.

Isometric muscle force is a critical factor in many daily activities such as standing and grasping and therefore effort is justified in trying to reduce isometric fatigue. We chose to investigate fatigue in isometric conditions for several reasons. First, it is the easiest condition to control experimentally. Secondly, it is desirable to limit the number of factors, such as stretch velocity and different muscle lengths, so as not to confound the results with too many dimensions.

Subjects with previous FES training demonstrated no particular resistance to fatigue when compared to subjects with no previous FES experience. This was a somewhat surprising result, but we had no indication of how intensive the subjects' FES applications had been.

Conclusions

Despite significant efforts to reduce and eliminate the problem of muscle fatigue associated with FES, it remains a major limitation for applications of FES such as walking and grasping. Random modulation of frequency, amplitude and pulse width during stimulation did not appear to have any effect on the fatigue rate of isometric contractions of the quadriceps and tibialis anterior muscles of subjects with complete SCI. Therefore, we conclude that these are not viable techniques for fatigue reduction in practice. Rest periods of ten minutes were found to be insufficient to allow complete restoration of muscle strength between stimulation trials.

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TABLE 1: Summary of subject data

Subject	Age (years)	Level of Injury	Injury duration (years)	Prior FES Training
1	26	T2/T3	9	Surface Stim 3 months
2	27	T7	0.25	none
3	24	C6/C7	8	none
4	31	C6/C7	7	none
5	29	T4	3	FES bike 1 year
6	38	C7	13	none
7	39	T8	10	Surface Stim 1 year
Average	30.6		7.2	
Standard Dev	5.9		4.3	
Minimum	24	T8	0.25	none
Maximum	39	C6/C7	13	1 yr

TABLE 2: Summary of statistical results from all hypothesis tests

Repeated measures ANOVA	Threshold (%)	*p-value*	
		Stim. effect	Order effect
Fatigue time	60	0.336	0.117
	70	0.329	0.229
	80	0.503	0.372
FTI	60	0.415	0.119
	70	0.414	0.218
	80	0.549	0.373
Maximum Force		0.304	**0.0003**

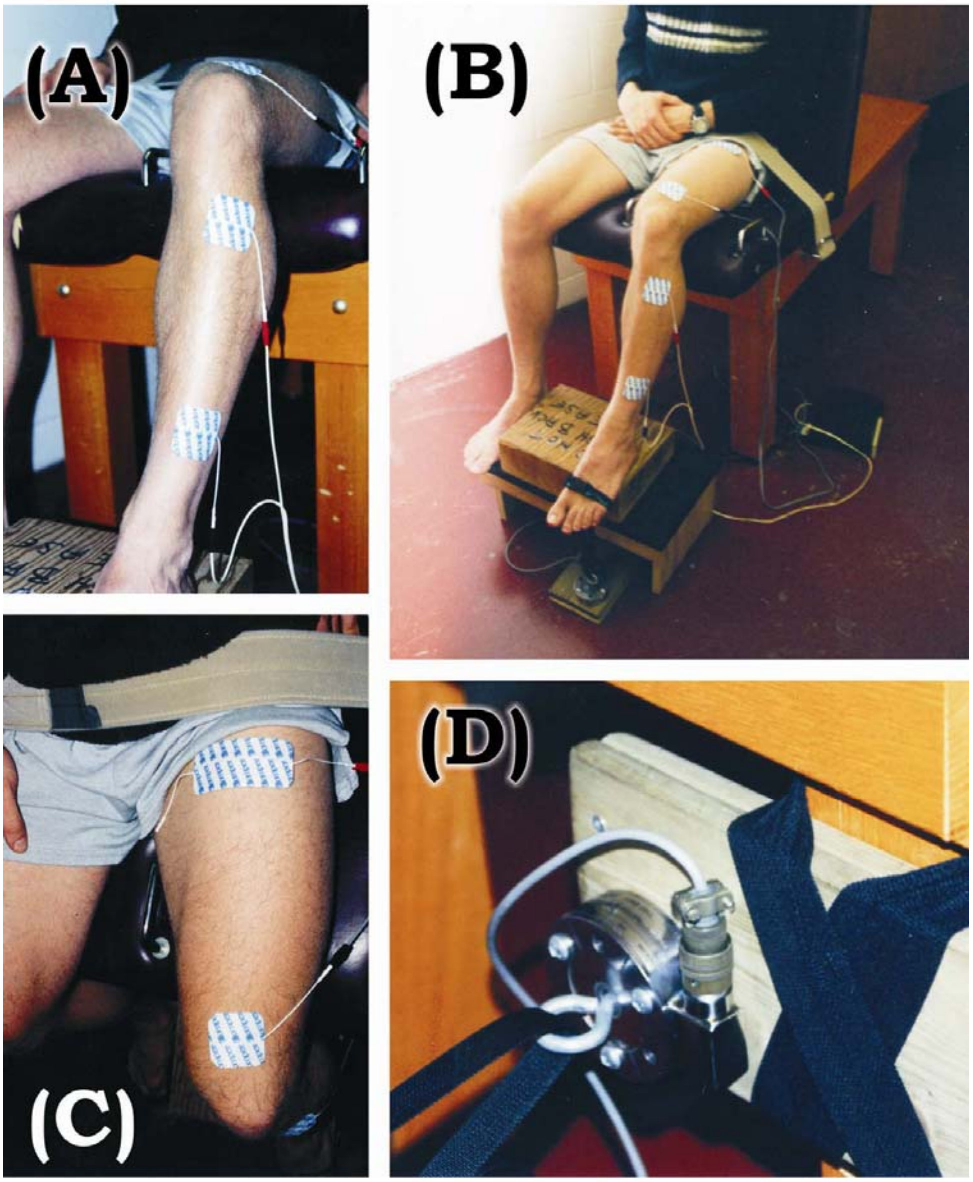

Figure 1: Photos of the electrode placement on the (A) anterior tibialis and (C) quadriceps, showing the active electrodes located proximally and the reference electrodes located distally. (B) shows the upright sitting position of each subject on the padded bench. (D) shows the strain gauge load cell used to measure force. The person in this figure is able-bodied and was only used to demonstrate the experimental setup.

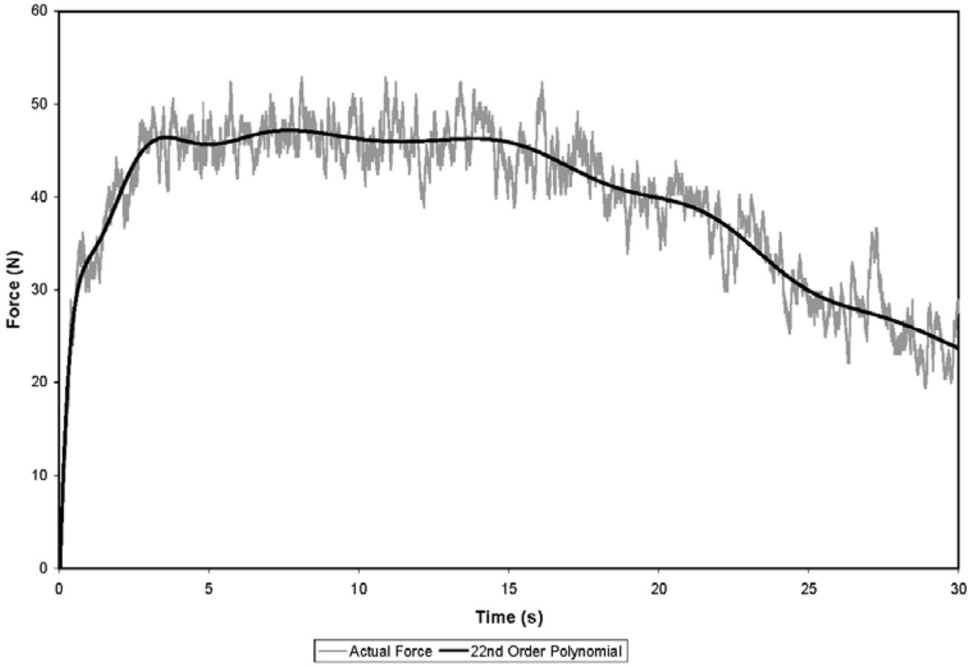

Figure 2: Force-time curve for stimulation of subject three’s right tibialis with amplitude randomization. There are peaks at approximately 3.6, 7.6, and 13.8 seconds.

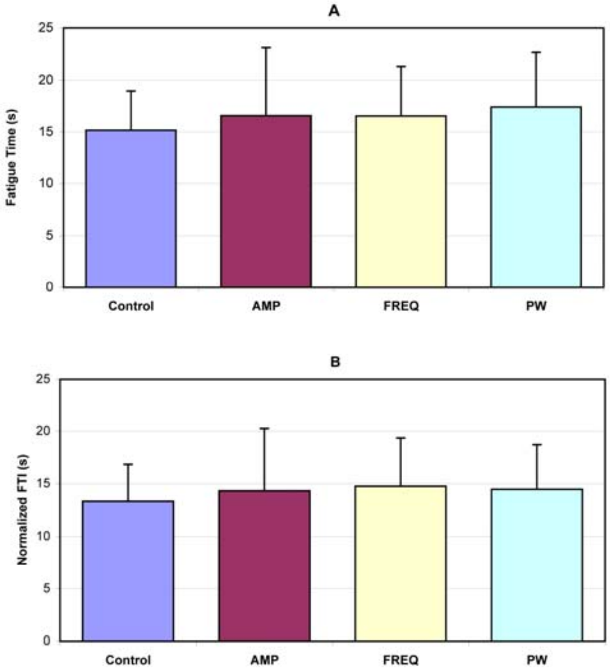

Figure 3: Average values over all muscles of fatigue time and FTI for the four treatment groups: Constant stimulation (Control), amplitude modulation (AMP), frequency modulation (FREQ), and pulse width modulation (PW). P-value > 0.05 for all tests.

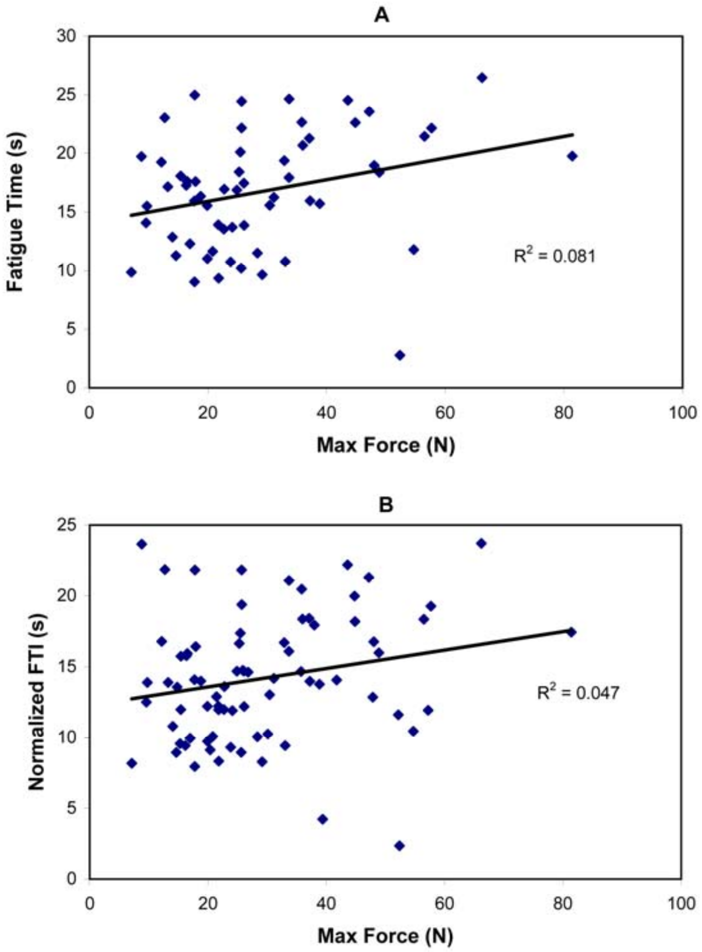

Figure 4: Linear correlation between (A) fatigue time and maximum force ($R^2 = 0.081$), and (B) FTI and maximum force ($R^2 = 0.047$)

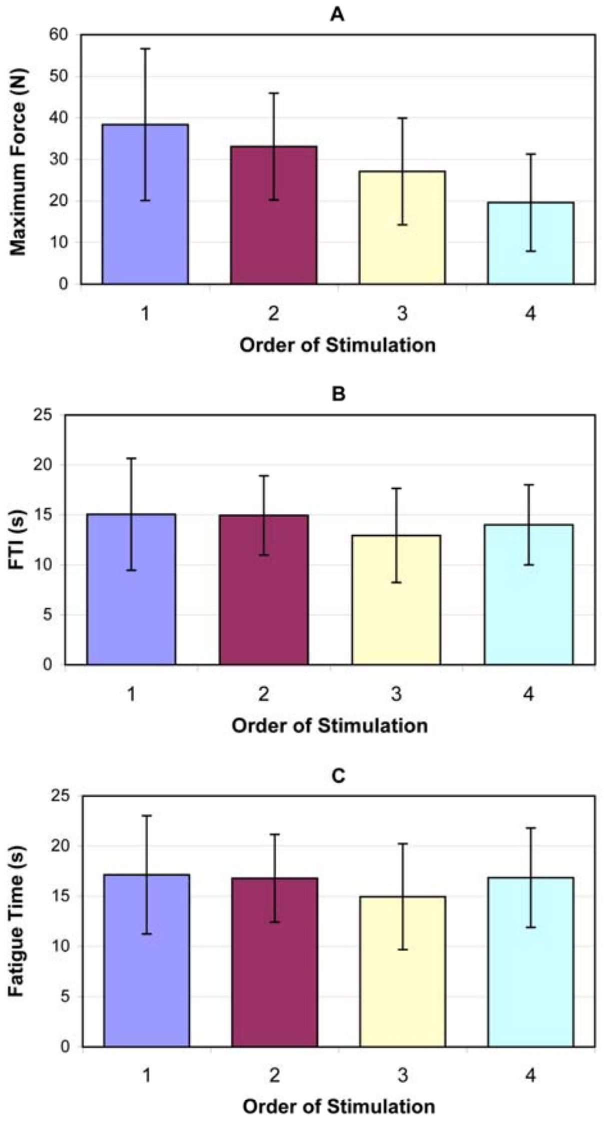

Figure 5: The maximum force, FTI, and fatigue time data averaged for all subjects for the 1st, 2nd, 3rd, and 4th trial. Stimulation order appeared to have no effect in terms of fatigue time or FTI, however it had a clear, diminishing effect on maximum force ($p<0.0001$). Error bars indicate ± one standard deviation.