

1 **TITLE PAGE**

2 **The Central Nervous System Modulates the Neuromechanical Delay in a Broad Range for the Control**
3 **of Muscle Force**

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6 **Abbreviated title:** Introducing the Neuromechanical Delay

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21 Electromechanical delay; Neural Drive; Motor unit; Force Prediction; Sinusoidal Contractions;

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27 **ABSTRACT**

28 Force is generated by muscle units according to the neural activation sent by motor neurons. The motor unit
29 is therefore the interface between the neural coding of movement and the musculotendinous system. Here
30 we propose a method to accurately measure the latency between an estimate of the neural drive to muscle
31 and force. Further, we systematically investigate this latency, that we refer to as the neuromechanical delay
32 (NMD), as a function of the rate of force generation. In two experimental sessions, eight men performed
33 isometric finger abduction and ankle dorsiflexion sinusoidal contractions at three frequencies and peak-to-
34 peak amplitudes [0.5,1,1.5 (Hz); 1,5,10 of maximal force (%MVC)], with a mean force of 10% MVC. The
35 discharge timings of motor units of the first dorsal interosseous (FDI) and tibialis anterior (TA) muscle were
36 identified by high-density surface EMG decomposition. The neural drive was estimated as the cumulative
37 discharge timings of the identified motor units. The neural drive predicted $80 \pm 0.4\%$ of the force fluctuations
38 and consistently anticipated force by 194.6 ± 55 ms (average across conditions and muscles). The NMD
39 decreased non-linearly with the rate of force generation ($R^2 = 0.82 \pm 0.07$; exponential fitting) with a broad
40 range of values (from 70 to 385 ms) and was 66 ± 0.01 ms shorter for the FDI than TA ($P < 0.001$). In
41 conclusion, we provided a method to estimate the delay between the neural control and force generation and
42 we showed that this delay is muscle-dependent and is modulated within a wide range by the central nervous
43 system.

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45 **New & Noteworthy**

46 The motor unit is a neuromechanical interface that converts neural signals into mechanical force with a delay
47 determined by neural and peripheral properties. Classically, this delay has been assessed from the muscle
48 resting level or during electrically elicited contractions. In the present study we introduce the
49 neuromechanical delay as the latency between the neural drive to muscle and force during variable-force
50 contractions, and we show that it is broadly modulated by the central nervous system.

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56 INTRODUCTION

57 Movement is the result of the interaction between neural and muscular structures. Neuromechanics aims at
58 understanding the functional effects of the neural coding of movement. The motor unit is the interface
59 between neural coding (by motor neurons) and force generation (by muscle units). The conversion of neural
60 code to force has a latency due to the dynamic sensitivity of the motor neurons (1) and to the time needed to
61 stretch the series elastic components (SEC) of the muscle-tendon unit following the depolarization of the
62 muscle fibers (19, 22).

63 Estimates of the electromechanical delay (EMD) have been obtained during voluntary and electrically-elicited
64 contractions (18, 25, 29, 30) or in isolated animal preparations (1). However, these methods do not provide
65 information on the delay between neural drive to muscles and force during contractions with force
66 modulation since they are obtained from the muscle resting state or during electrically-induced contractions
67 (1, 4, 19, 22, 28). Moreover, with these approaches it is not possible to investigate the potential task-
68 dependent changes of EMD. Indeed, it is generally believed that the EMD is a constant property of a muscle
69 (19, 22).

70 The estimates of EMD are significantly greater when they are obtained during voluntary force generation
71 than electrically-elicited contractions (25, 30). This indicates that the EMD depends on the properties of the
72 recruited motor units. Since the motor unit twitch properties vary widely within a muscle (5, 17), we
73 hypothesized that the delay between neural drive to muscle and force varies within a large range of values
74 during voluntary tasks. Because of technical limitations, an estimate of the delay between neural drive to
75 muscle and force across conditions has not been previously possible.

76 Here we define the neuromechanical delay (NMD) as the latency between the neural drive to muscle and
77 force during voluntary contractions of variable force and we propose an accurate methodology for its
78 estimation across a broad range of conditions. Further, we test the hypothesis that the central nervous
79 system (CNS) modulates the NMD in a wide range of values. The results provide evidence of a functional
80 tuning of the NMD by the CNS.

81 METHODS

82 Eight moderately active men participated to the experiments (age 27.2 ± 2.2 year; body mass 79.5 ± 2.5 kg;
83 height 178.4 ± 6.5 cm). The experiments were approved by the Ethical Committee of the Universitätsmedizin
84 Göttingen, approval n. (1/10/12). Before taking part in the testing measurements an informed written consent
85 was signed by all subjects. None of the subjects reported any history of neuromuscular disorders or upper
86 limb pathology or surgery.

87 *Experimental Design*

88 Experiments for the upper and lower limb were performed in two days separated by one week. In each
89 experiment, the participants performed three isometric index finger-abduction maximal voluntary contractions
90 (MVC) or three isometric ankle-dorsiflexion MVC with their dominant limb (self-reported) and nine trials of
91 isometric sinusoidal force contractions at different amplitudes and frequencies. The joint force signal was
92 visualized on a monitor positioned directly in front of the subjects. The MVC feedback and sine wave
93 trajectories were displayed through a custom MATLAB script (MathWorks, Inc., Natick, Massachusetts,
94 USA). During the MVC, the participants were verbally encouraged to 'push as hard as possible' for at least 3
95 s. The maximal MVC value was recorded and used as a reference value for the sinusoidal isometric
96 contractions. Participants were asked to track sinusoidal force trajectories at the frequencies 0.5, 1, or 1.5 Hz
97 and amplitudes 1, 5, or 10% MVC, in all combinations (9 tasks in total), for 2 min. The mean level of the
98 target trajectories was 10% MVC. The 9 tasks were performed in a random order with a recovery time of 3
99 min between tasks.

100 *Force and EMG recordings*

101 For the finger abduction experiments, participants comfortably seated with the dominant arm (self-reported)
102 placed in a custom-made isometric dynamometer that immobilized the forearm and restrained the wrist and
103 fingers. Isometric force during finger abduction was measured by a strain gauge that was positioned
104 perpendicular to the index finger. This setup allowed recording the force directly arising from the abduction of
105 the finger. For the ankle dorsiflexion measurements, participants were seated in an isometric dynamometer
106 Biodex System 3 (Biodex Medical System Inc., Shirley, NY, USA) in an upright position, with the dominant
107 leg (self-reported) extended and the ankle flexed at 30° with respect to neutral position. The ankle joint and
108 the foot were fastened with Velcro straps. High-density surface electromyography (HDsEMG) signals were
109 recorded from the first dorsal interosseous muscle (FDI) or the tibialis anterior muscle (TA) in each session
110 by using a grid of 64 electrodes (5 columns, 13 rows; gold-coated; 2-mm diameter (FDI), 4-mm diameter
111 (TA); interelectrode distance: 4 mm (FDI), 8 mm (TA); OT Bioelettronica, Torino, Italy). Before placing the

112 HDsEMG grid, the skin was shaved, lightly abraded and cleansed with 70% ethanol. The electrode grid was
113 placed on the skin with a conductive paste (SpesMedica, Battipaglia, Italy) that established the skin-
114 electrode contact. HDsEMG signals were recorded in monopolar derivation (3-dB bandwidth 10-500 Hz;
115 EMG-USB2+ multi-channel amplifier, OT Bioelettronica, Torino, Italy) and digitally converted on 12 bits at
116 2048 samples/s. The EMG and joint torque were concurrently recorded by the same acquisition system.

117 *High-density EMG decomposition*

118 The HDsEMG signals were digitally filtered with a band-pass filter at 20-500 Hz (2nd order, Butterworth).
119 Then they were decomposed into the activity of individual motor units with an extensively validated
120 decomposition algorithm (13, 15, 21, 26). Motor units with a pulse-to-noise ratio (14) less than 30 dB and/or
121 with discharges separated by more than 2 s were discarded from further analysis. The individual motor unit
122 discharge timings were summed to generate a cumulative spike train (CST). The CST is an estimate of the
123 neural drive sent to the muscle (9, 20). Since the number of discharges per second in the CST depends on
124 the number of decomposed motor units, we further calculated the average number of discharges per motor
125 unit per second, as the number of discharges in the CST per second divided by the number of decomposed
126 motor units (DR, s⁻¹).

127 *NMD estimation*

128 We defined the NMD as the time delay between the rise time of the motor unit action potentials and the
129 respective force output identified by the cross-correlogram. For the computation of the delay between neural
130 drive and force, a band-pass filter (bandwidth 2 Hz) was applied to the CSTs and force signals (4th order
131 zero-phase Butterworth filter). After filtering, the CST and force signals were divided into one-cycle time
132 frames and the cross-correlation between CST and force was computed for each time frame and then
133 averaged across all time frames. The time lag of the peak of the cross-correlation function provided an
134 estimate of the NMD. The estimated NMD was associated to frequency and amplitude of the sinusoidal
135 contractions as well as to the maximum rate of change of force, i.e. the first derivative of force (proportional
136 to the product of amplitude and frequency). Finally, the force and trajectory profiles were cross-correlated to
137 assess the force tracking accuracy.

138 *Statistical Analysis*

139 A three-way (2 muscles x 3 frequencies x 3 force levels) repeated measures ANOVA was computed for the
140 NMD and the estimated force accuracy. When an interaction was found, a Bonferroni correction was applied

141 to account for multiple comparisons. Finally, linear and non-linear regression was used to fit the values of
142 NMD and DR as a function of the force derivative. Data are reported as mean \pm SD. The significance level
143 was set to $P < 0.05$.

144 RESULTS

145 *High-density EMG decomposition*

146 The total number of decomposed motor units for all subjects and conditions was 1170 for the FDI and 3357
147 for the TA muscle. The average number of identified motor units for each subject and condition was $8.66 \pm$
148 3.27 and 21.3 ± 5.34 for the FDI and TA, respectively.

149 *Neuromechanical delay*

150 There was no difference in the force tracking accuracy between muscles ($R=0.68 \pm 22.67$ and $R=0.68 \pm$
151 21.09 , for FDI and TA; $P>0.05$). However, the increase in frequency determined a decrease in the tracking
152 accuracy for both the FDI and TA muscle ($R= 85.9 \pm 7.14$, 79.5 ± 4.69 , 41.3 ± 4.33 for FDI, and $R= 85.6 \pm$
153 8.45 , 77.2 ± 5.05 , 41.3 ± 3.84 , for TA, for 0.5, 1, and 1.5 Hz, respectively).

154 Figure 1 shows a representative example of estimation of NMD. At the group level, the filtered CST predicted
155 $83 \pm 0.20\%$ and $76 \pm 0.14\%$ of the force fluctuations for the FDI and TA muscle, respectively. The latency
156 between the CST and force ranged from 70 ms to 334 ms for the FDI and from 138 ms to 385 ms for the TA,
157 depending on the task. The NMD was significantly smaller for the FDI than the TA muscle [average across
158 conditions, 164.5 ± 60 ms vs. 224.7 ± 50 (ms), ANOVA, $P<0.001$].

159 Figure 2 shows the average latency for all subjects at each target amplitude and frequency of the sinusoid.
160 The increase in either frequency or amplitude determined a decrease in the NMD (ANOVA $p<0.001$). The
161 NMD values were consistently greater during the low-force slow-oscillation tasks than for larger and faster
162 oscillations. The shortest NMD corresponded to the highest target frequency and peak-to-peak amplitude
163 (1.5 Hz; 10 %MVC). At the same relative target amplitudes, the change in the frequency of the sine wave
164 decreased the NMD significantly (Fig. 2). An example is represented in Figure 1 that shows that at the same
165 relative peak-to-peak amplitude of 5% (MVC), a change in frequency from 0.5 Hz to 1 Hz determined a
166 decrease in NMD by approximately 50 ms. These results were confirmed by the group analysis (Figure 2).
167 For example, when the peak-to-peak amplitude of the sine wave was 1% MVC, the NMD decreased
168 significantly as a function of frequency, with a mean difference of 134.4 ± 33.5 (ms) and 143.6 ± 16.2 (ms)

169 between 0.5 and 1.5 Hz, for the FDI and TA muscle respectively. This indicated that the NMD varied widely
170 when generating the same forces at different rates of force generation.

171 Overall, the NMD in the two muscles changed as a function of both frequency and amplitude. The analysis of
172 the force derivative (slope) (Fig. 3) indicated a strong association of the NMD with the product of frequency
173 and amplitude (i.e., speed of the contraction). The NMD decreased in a non-linear way with an increase in
174 contraction speed (Fig. 3).

175 *Discharge rate*

176 The average motor unit discharge rate ranged from 1.18 to 17.66 pps (FDI) and from 1.03 to 12.22 pps (TA),
177 with average values across all conditions of 9.06 ± 4.15 pps (FDI) and 8.50 ± 2.62 pps (TA). The average
178 motor unit discharge rate was negatively associated to the rate of change of force ($R^2 = 0.95$ ($p < 0.001$) and
179 $R^2 = 0.75$ ($p < 0.01$) for the FDI and TA respectively). This negative association indicates a decrease in the
180 average number of discharges per motor unit with an increase in speed of the contraction.

181 **DISCUSSION**

182 We have defined the NMD as the time difference between the neural command to muscle and the generated
183 force during voluntary tasks. An estimate of the NMD can be obtained from the time lag of the peak of the
184 cross-correlation between an estimate of the neural drive and force. The estimated NMD was on average
185 ~200 ms and was modulated by the CNS according to the contraction speed. The NMD is intrinsically related
186 to the motor unit twitch properties and can thus be modulated following the size principle.

187 *Estimate of the neuromechanical delay*

188 For both muscles, the correlation between the estimated neural drive and force was on average >75%,
189 indicating accurate EMG decomposition over relatively large motor unit populations and robust delay
190 estimation. Conversely, previous studies that cross-correlated individual motor unit discharge timings with
191 force during sinusoidal contractions reported values of correlation <10% (7). The high correlation values in
192 this study allowed us to define a robust estimate of the delay whereas the mathematical definition of a delay
193 does not hold for low correlation values (since two signals of different shape cannot be seen as delayed
194 version of each other). Since the CST represents common input components shared between motor neurons
195 (8), the identification of a relatively large number of motor units improved the prediction of force fluctuations
196 and the accuracy in delay estimates (20).

197 *Factors determining the NMD*

198 The motor unit recruitment pattern is related to the biophysical properties of the motor neurons. Motor unit
199 properties vary widely in a muscle and depend on the recruitment threshold of the motor neuron (2, 5, 12,
200 26, 27). The wide distribution of properties of motor units in an individual muscle explains the possibility of
201 modulating the NMD.

202 Because the NMD depends on the dynamic sensitivity of the motor neurons (1) and the intrinsic properties of
203 the musculotendinous system, the CNS can modulate the NMD only by varying the activation of muscle
204 units. This activation is constrained in order by the size principle (11). However, the motor unit recruitment
205 thresholds depend on the rate of force development (6, 24). Therefore, the NMD can be modulated by tuning
206 the recruitment thresholds, maintaining the ordering by size. The recruitment of motor neurons depends on
207 the net excitatory input they receive (10). The need for generating faster contractions determines a decrease
208 in recruitment threshold so that a greater number of motor units is recruited for the same force. This
209 compressed recruitment range is compensated by a decrease in the average discharge rate per motor unit,
210 as shown in Fig. 4. The underpinning mechanisms determining a decrease in the NMD with frequency and/or
211 amplitude of the sinusoid thus differ. The amplitude of sinusoidal force contractions is increased by
212 recruitment and increased discharge rate while the frequency is increased by a compressed recruitment and
213 a decrease in average discharge.

214 The association between motor unit twitch properties and NMD is also confirmed by the differences found
215 between FDI and TA. The full motor unit recruitment for the FDI and TA muscle differs. The FDI motor units
216 are fully recruited at ~50% MVC (16), whereas the pool of motor units innervating the TA muscle completes
217 recruitment at ~90% MVC (5). Thus, at the same relative force, the FDI recruits relatively larger motor units
218 (with faster twitches) compared to the TA. Although previous evidence from individual motor unit measures
219 of twitch tension and contraction times indicate relatively similar mechanical properties for these two muscles
220 (3, 5), the muscle fiber composition and tendon stiffness may also contribute to the differences in NMD. In
221 animal preparations, when stimulating motor neurons with sine waves, the delay between stimulation and
222 force (equivalent to our NMD) decreases with increasing stimulation frequency due to the dynamic sensitivity
223 of the motor neurons (1). Moreover, the slow twitch motor units tend to have a shorter NMD when compared
224 to the fast ones (1). Indeed, sine-wave stimulations of cat soleus axons shows a smaller NMD when
225 compared to the gastrocnemius muscle due to slower rise time of soleus motor unit twitches (23).

226 The proposed approach provides a precise analysis of the delay that the CNS experiences in providing
227 neural command to the muscles during force modulation in humans. This analysis allows the establishment
228 of a functional link between the neural and muscular mechanisms of force generation. The decrease in NMD
229 with the rate of force generation presumably serves the functional purpose of optimising the force control
230 accuracy. The tracking accuracy decreased with an increase in the frequency of the sine-wave in this study
231 but the decrease was relatively limited, likely due to a shorter control delay. A shorter delay between neural
232 command and force generation indeed implies a larger bandwidth of control, extending the functional range
233 of accurate motor tasks to faster movements. This may be specifically relevant for hand muscles that require
234 precise control for fast and dexterous hand tasks. Indeed, our results showed a large difference in NMD
235 between a hand and a leg muscle. From the functional view, the time delay that the CNS experiences
236 between neural commands and force generation continuously changes over time during natural tasks,
237 according to the instantaneous changes in speed of the task. This variation is not determined by a direct
238 modulation but is the result of the distribution of muscle unit properties and of the intrinsic properties of motor
239 neurons. This tuning presumably allows optimal control over a large range of conditions without any
240 cognitive effort. Nonetheless, despite the smaller NMD observed for the FDI muscle, we did not detect any
241 differences in the tracking accuracy between the two muscles. This contradictory observation should be
242 analysed in further studies.

243 *Neuromechanical and electromechanical delay*

244 The defined NMD is very different from the classic EMD. Indeed, the NMD is the delay between neural drive
245 and force during tasks with any rate of force variations while the EMD is measured from the interference
246 EMG (“electro”, not “neuro”) at the instant of sudden force changes (e.g., during ballistic or electrically
247 elicited contractions). Classic EMD values are considerably shorter when compared to our results on NMD.
248 EMD estimates are obtained as the time difference between the onset of the surface EMG signal and the
249 onset of force. During electrical stimulation, the EMD in the gastrocnemius muscle is only ~15 ms (19, 22).
250 During voluntary contractions from the muscle resting state, the EMD is ~38 ms in the vastus lateralis (ms)
251 (and ~17 ms in the same muscle during electrical stimulations) (30). The estimates of EMD were found
252 slightly greater, although still smaller than the currently estimated NMD, for the biceps brachii muscle during
253 voluntary fast contractions starting from a baseline level (~70 ms) (28). The reason for the different estimates
254 of EMD with respect to our NMD are not only related to the use of the EMG but, mainly, to the type of
255 contractions used for the estimate.

256 The NMD is influenced by the time to peak of the twitches of the active motor units that range widely within a
257 muscle (e.g., 51 to 114 ms for the TA muscle (5)). Therefore, the active part of the SEC in single motor units
258 significantly contributes to the NMD. This finding is in disagreement with previous examinations of the
259 determinants of EMD during electrically induced contractions. These previous studies indicate that 52% of
260 the EMD depends on the properties of the aponeurosis and the tendon (i.e., the non-active part of the SEC)
261 (22), with the tendon slack contributing significantly to the EMD (19). The NMD in the present study was
262 largely modulated by the CNS by recruitment of motor units rather than being influenced by the non-active
263 part of the SEC. Indeed, at similar frequencies and peak-to-peak amplitudes of the sinusoidal forces as in
264 the present study, the NMD was significantly smaller when compared to a continuous stretch of the muscle-
265 tendon unit (1 %MVC, 1 Hz). Finally, sine wave stimulations of motor axons or individual motor neurons in
266 animal studies also show large estimates of NMD, similar to the present study (1, 23).

267

268 Conclusion

269 We proposed a novel method to accurately estimate the delay between the neural code and the mechanics
270 of muscle contraction during voluntary tasks, defined here as NMD. Previous studies determined an EMD
271 during electrically-induced contractions or from a resting condition that provide results dissociated from the
272 actions of the CNS during functional force modulation. The NMD ranged broadly and was associated to the
273 rate of force development, so that faster contractions were performed with shorter NMD. These results
274 indicate that the NMD is intrinsically related to the recruitment of motor units with a wide range of mechanical
275 properties, so that it can be modulated broadly within the constraints of the size principle.

276

277 Conflict of interest

278 The authors declare no competing financial interests

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366 **FIGURE CAPTIONS**

367 **Figure 1**

368 **A.** Motor unit discharge timings identified from surface EMG decomposition during an isometric sinusoidal
369 contraction of the tibialis anterior muscle at a frequency of 0.5 (Hz) and a peak-to-peak amplitude of 5%
370 MVC. **a.** Discharge timings of motor units of the same muscle during a contraction at the frequency of 1 Hz
371 and same amplitude as in **A**. The black line in **A** and **a** represents the force during the sinusoidal force
372 contractions in percentages of MVC. Each colour represents the discharge timings of an individual motor unit
373 **B. and b.** The force signal and the motor unit discharge timings reported in **A-a** were low-pass filtered (2 Hz)
374 in order to generate the smoothed discharge rate for each motor unit in **B. and b**. The smoothed motor unit
375 spikes show a high degree of correlation with force. Moreover, it can be noted that they consistently
376 anticipate the force for all the decomposed motor units. **C-c.** The individual motor unit discharge timings
377 were summed in order to generate the cumulative spike trains (CST). After summation, the CST was filtered
378 with a 2 Hz low-pass filter. The filtered CST and the force signal were cross-correlated in order to estimate
379 the neuromechanical delay (NMD). Despite the force traces in the two cases have the same peak-to-peak
380 amplitude, the greater frequency of force oscillation corresponds to a shorter NMD, that can be visually seen
381 by comparing the epoch length between two green lines in **C and c**. **D-d.** and **E-e.** represent the same
382 sinusoidal contraction in **A** and **a** but for the full duration of the task (2 min). **D-d.** A representative example
383 of computation of the NMD as time lag of the peak of the cross-correlation function between the CST and the
384 force signal for the full duration of the task. **E-e.** The cross-correlogram for the target sinusoid at 0.5 (Hz) and
385 amplitude of 5% MVC (**E**) and the sine-wave at 1 (Hz) in (**e**) for the total length of the trial. The red dots are
386 centred at the correlation peak (~0.8 correlation coefficient) and the position of the peak corresponds to the
387 delay that is shown in **F** and **f**.

388 **Figure 2**

389 Estimates of the neuromechanical delay (NMD) as a function of the frequency of the force sinusoid for the
390 first dorsal interosseous (**A**) and tibialis anterior muscle (**B**). Each colour represents a different peak-to-peak
391 amplitude of the sinusoidal force trajectory. The black lines indicate significant differences at $P < 0.05$.

392 **Figure 3**

393 The estimated neuromechanical delay (NMD) as a function of the maximum force derivative (maximum rate
394 of change of force) for the first dorsal interosseous **(A)** and tibialis anterior muscle **(B)**. The force derivative
395 depends on the product of the amplitude and frequency of the sinusoidal force trajectory and indicates the
396 rate of force generation.

397 **Figure 4**

398 The average number of discharges per motor unit (total number of discharges across the detected motor unit
399 population, divided by the number of detected motor units and by time) as a function of the maximum force
400 derivative (maximum rate of change of force) for the first dorsal interosseous **(A)** and tibialis anterior muscle
401 **(B)**.

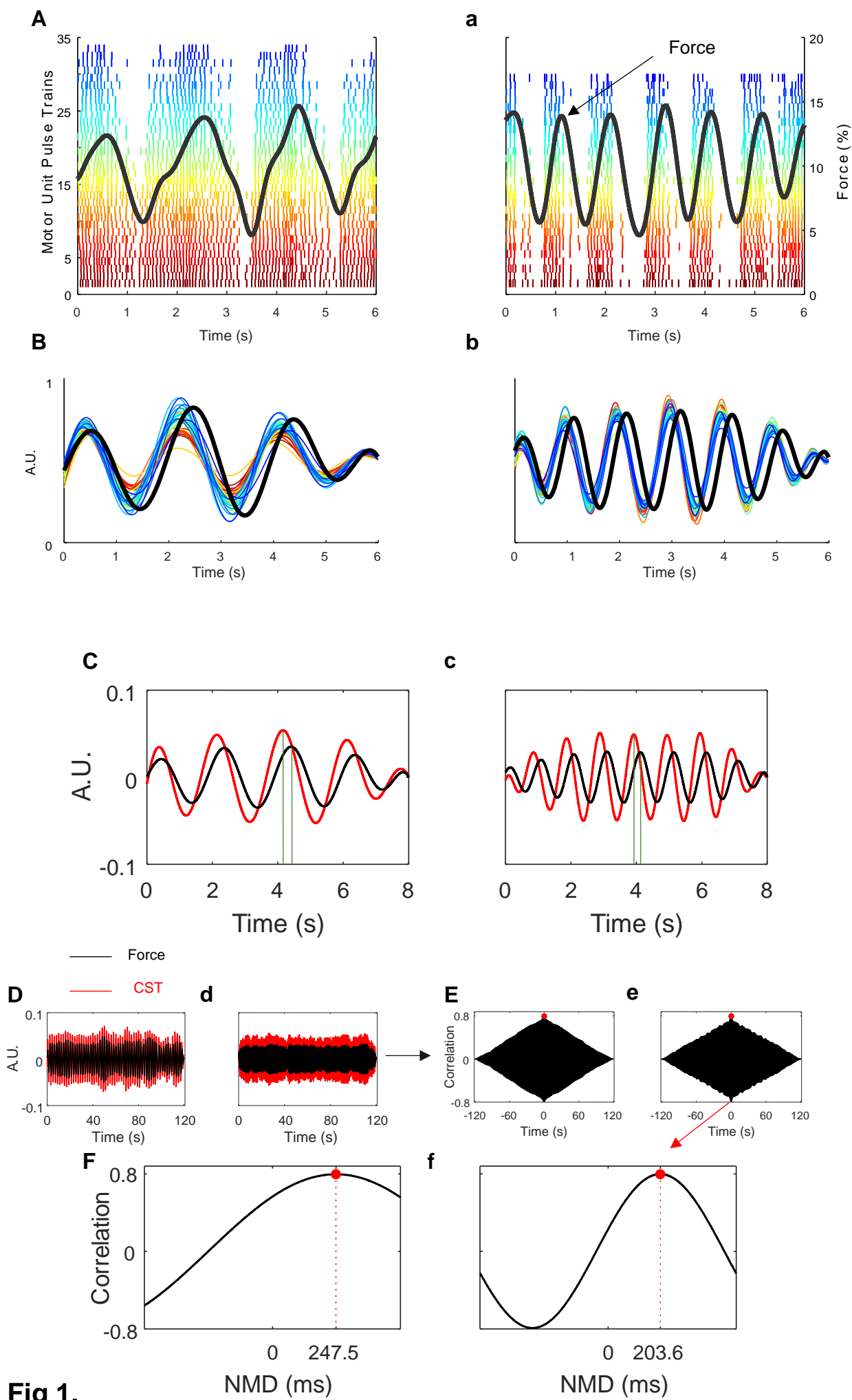


Fig 1.

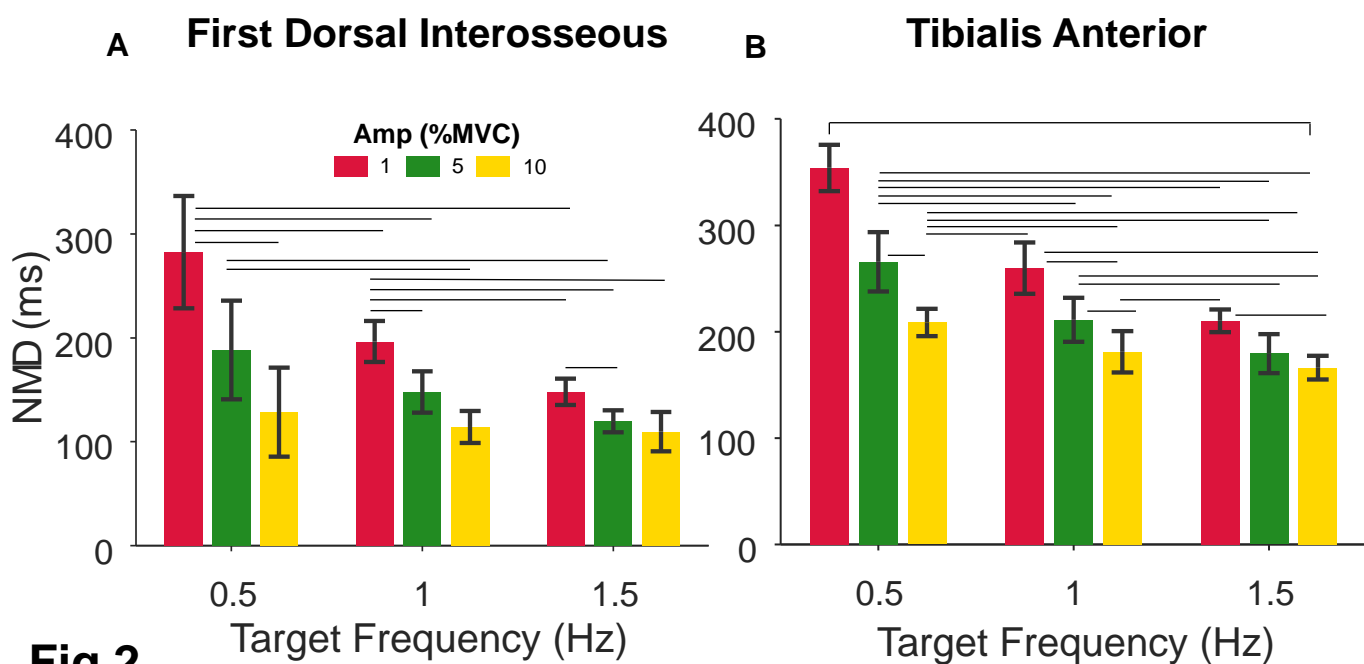


Fig 2.

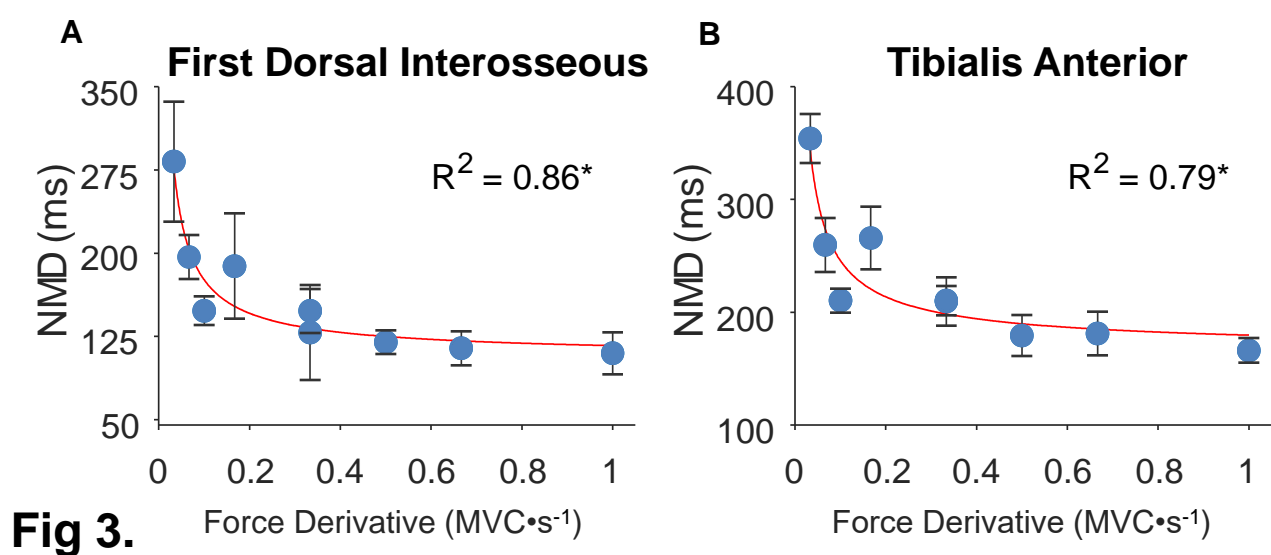


Fig 3.

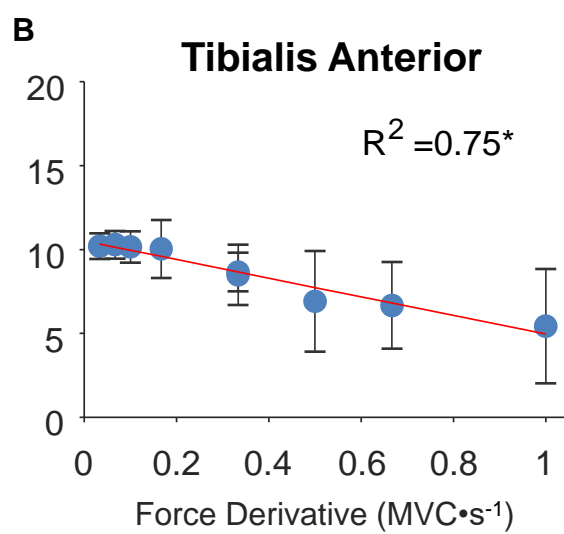
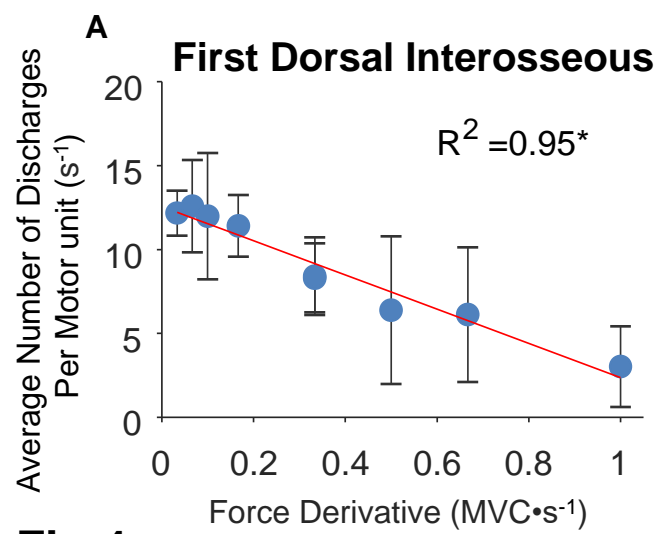


Fig 4.