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The relative strength of common synaptic input to motor neurons is not a determinant of the maximal rate of force development in humans

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ABSTRACT

Correlation between motor unit discharge times, often referred to as motor unit synchronization, is determined by common synaptic input to motor neurons. Although it has been largely speculated that synchronization should influence the rate of force development, the association between the degree of motor unit synchronization and rapid force generation has not been determined. In this study, we examined this association by both simulations and experimental motor unit recordings. The analysis of experimental motor unit discharges from the tibialis anterior muscle of 20 healthy individuals during rapid isometric contractions revealed that the average motor unit discharge rate was associated with the rate of force development. Moreover, the extent of motor unit synchronization was entirely determined by the average motor unit discharge rate ($R > 0.7$, $P<0.0001$). The simulation model demonstrated that the relative proportion of common synaptic input received by motor neurons, which determines motor unit synchronization, does not influence the rate of force development ($R = 0.03$, $P>0.05$). Nonetheless, the estimates of correlation between motor unit spike trains were significantly correlated with the rate of force generation ($R>0.8$, $P<0.0001$). These results indicate that the average motor unit discharge rate, but not the degree of motor unit synchronization, contributes to most of the variance of human contractile speed among individuals. In addition, estimates of correlation between motor unit discharge times depend strongly on the number of identified motor units and therefore is not indicative of the strength of common input.

New & Noteworthy

It is commonly assumed that motor unit synchronization has an impact on the rate of force development of a muscle. Here we present computer simulations and experimental data of human tibialis anterior motor units during rapid contractions that show that motor unit synchronization is not a determinant of the rate of force production. This conclusion clarifies the neural determinants of rapid force generation.

INTRODUCTION

Human motor neurons receive common and independent synaptic inputs from supraspinal and spinal circuitries (13, 15, 26, 35). These inputs are shared between motor neurons that innervate an individual muscle (26, 34, 35) or synergistic muscles (14, 20, 25, 27), and partly determine the synchronization of discharges of motor units identified by the electromyogram (12). During postural tasks of the hand and lower limb, the common synaptic input in the bandwidth responsible for force control (<5 Hz) largely modulates the force fluctuations around a fixed target. Accordingly, an increase in variance of the common synaptic input contributes to a decrease in force steadiness which occurs with ageing (1, 16).

Although many studies have examined common synaptic input to motor neurons during steady isometric contractions, there are no reports during fast contractions. Consequently, our understanding of the neural determinants of contractile speed is largely indirect (17, 28, 36, 44), with very few studies examining motor neuron behavior during fast voluntary movements (5, 8, 47). Nevertheless, the neural input to muscle during rapid contractions is a critical determinant of neuromuscular performance and therefore knowledge in this area is relevant in many fields, ranging from athletic performance to prevention of falls and injury (28).

We recently showed that the speed of human movement during single-joint contractions depends on the initial motor neuron discharge rate (47). Nonetheless, many have hypothesized that greater motor unit synchronization may also contribute to an increase in the rate of force development and to the associated changes in rate of force production with training (2, 23, 29, 38, 39). Although this speculation seems intuitively correct, no study has experimentally tested the correlation in spike times of motor units during rapid contractions.

During rapid contractions, motor neurons are recruited in very short time intervals and discharge at high frequencies (>100Hz) (5, 47). In these conditions, the measures of motor unit synchronization might be

significantly influenced by the discharge rate. Recent experimental data and simulation models have indeed shown that the correlation between motor unit discharge times depends on the discharge rate (11, 34). Therefore, motor unit synchronization is intrinsically related to the number of discharged action potentials while it may not have a functional impact on force generation (11). In this study, we will refer to motor unit synchronization to indicate the absolute correlation value between the population of motor unit discharge times as estimated via the cross-correlation function (35). It has indeed been shown that normalization of correlation measures cannot compensate for the dependence of these measures on intrinsic motor neuron properties and discharge rate (31).

For the first time, we experimentally estimated the correlation in motor unit spike trains during isometric rapid contractions of the tibialis anterior muscle in twenty healthy volunteers. We show that even if motor unit discharge times show higher correlation at the beginning of the rapid contractions, this relatively high correlation is not a determinant of the rate of force development, but it is rather intrinsically associated to the high discharge rates. Further, a motor neuron simulation model showed that the relative strength of common vs independent input to motor neurons, which determines motor unit synchronization, does not influence the rate of force development and the correlation in the motor unit spike trains, confirming the experimental evidence. Finally, we provide evidence that the rate of force production is mainly associated to the discharge rate of motor neurons.

METHODS

Simulations

We simulated the activity of 188 motor neurons (49) with a leaky integrate-and-fire model. The force exerted by each motor unit was modelled using previously described equations (18) and the distribution of the absolute forces was obtained from previous experimental data on the tibialis anterior motor unit twitch forces (6).

Figure 1 shows the parameters of the model. Each neuron in the model received a synaptic input comprising a common component to all motor neurons and an independent synaptic noise for each

neuron, reflecting its unique connections. A similar approach has been previously used to model the common and independent input to pools of motor neurons (9, 13, 34). Since the aim of this work was to assess if the modulation of common input to all motor neurons was responsible for the increase in the rate of force development, we selected a relatively large range of common and independent synaptic inputs that reflected the variability in the discharge of human motor units (10-30 % coefficient of variation of interspike intervals (5, 30, 47)). The resting membrane potential was set at -70 (mV) and the spike threshold at -50 (mV), with a membrane time constant of 20 (ms).

The common and independent input components both had a bandwidth of 0-50 Hz. In the model, each cell received a mean current that followed an exponential decreasing curve similar to the observed output from in vitro (37) and in vivo (47) motor neurons and was in the range 6 to 16 nA. The maximum current was sufficient to recruit all motor neurons simultaneously, with delays depending on the axonal conduction velocities, that were modelled with an exponential distribution in the range 60-100 ms (4, 19). The absolute discharge rate values were within the experimentally observed physiological boundaries during rapid contractions in the human tibialis anterior, and ranged between 8 and 200 pps (5, 47). The decrease in motor neuron discharge rate varied in a range of ~40 pulses per second (pps) and decreased during the simulated rapid contractions, as experimentally observed (47). In all simulations, the variance (σ^2) in common synaptic noise was lower than the synaptic currents (6-16 nA) (34). The common and independent input received by motor neurons was simulated as previously described (34).

The discharge times of the motor neurons and the twitch force model were used to simulate the total muscle force as a linear summation of individual motor unit twitches (18). The model was implemented in MATLAB 2018b (MathWorks, Natick, USA), using optimized time steps of 1 ms. The analysis was limited to the first 100 ms from the onset of force, since the initial discharge rate (~first 40 ms from the onset of the first motor unit action potential) of motor neurons explains the variance in the maximal rate of force development in humans (47).

Experimental procedures

Twenty healthy, recreationally active men (24.9 (3.2) yr, 75.4 (8.6) kg, 180 (1.4) cm, 2636 (1298) metabolic equivalent min/week (International Physical Activity Questionnaire; IPAQ (3) with no history of

neuromuscular disorders participated in the study which was approved by the Ethical committee of the University of Rome “Foro Italico” (n. 44680). All participants were right leg dominant (self-reported). The study was conducted according to the Declaration of Helsinki and written informed consent was provided by the participants. The experimental procedures have been explained in detail previously (47).

Participants visited the laboratory on two occasions, separated by seven days, which consisted of a familiarization session followed by the experimental session. At the beginning of the first session, the participants completed the IPAQ to quantify their health-related physical activity. During the familiarization session, the participants were acquainted with the experimental protocol which involved isometric ankle dorsiflexion contractions. These contractions consisted of maximal voluntary contractions (MVCs), ballistic contractions (5, 7), and rapid isometric contractions (see below and (47)) with the force displayed on a monitor positioned at ~50 cm in front of the subjects. During the second session, high-density electromyography (HDsEMG) was acquired together with the force output from the dynamometer. The participants were asked to avoid strenuous exercise and caffeine consumption 48 h and 24 h respectively, before the experimental session.

The participants were instructed to perform the rapid contractions by contracting as fast and as forceful as possible after hearing an auditory cue and exceeding a visual target cursor on the monitor that was fixed at 75% MVC. When the target force was reached, the participants were asked to hold the force for 3 s. The participants were asked to avoid any countermovement and pre-tension before the onset of each rapid contraction.

The second session began with a warm-up of eight isometric submaximal dorsiflexion contractions (4 x 50%, 3 x 70%, 1 x 90% of perceived maximal voluntary force) of the dominant leg, each separated by 15 s, and three MVCs. Following the warm-up, a series of ballistic contractions were performed by the participants. The ballistic contractions consisted of fast isometric movements that required maximal activation but without maintaining the force. The participants were instructed to contract as fast and as forceful as possible and relax immediately after the peak force was reached. A minimum threshold of 75% MVC was set as the peak force during the short pulsatile contractions, and this was displayed on the screen for the participants. Following a rest of 4 min, the participants performed 12 isometric rapid

155 contractions that were divided in two blocks of six repetitions each. The contractions were separated by
156 20 s of rest and 2 min of rest was provided between each block.

157 *Force signal recordings*

158 A stiff custom-built ankle-ergometer was used in the familiarization and in the experimental session (OT
159 Bioelettronica, Turin, Italy). Participants were comfortably seated with the hip flexed to ~120° (180° =
160 neutral position) on a plinth with the dominant knee extended to ~180° (180° = neutral position) and the
161 ankle at ~100° (90° = neutral position) of plantar flexion. The foot was placed on a modifiable footplate
162 and the foot and ankle were firmly secured by Velcro straps. The foot strap (~3 cm wide) was located
163 over the distal portion of metatarsals, while the ankle strap (~3 cm wide) was secured on the foot dorsum,
164 perpendicular to the tibia. The latter was settled in series with a calibrated load cell (CCT Transducer
165 s.a.s, Italy), which was positioned vertical to the plantar surface of the foot. The force signal from the load
166 cell was amplified (x200) and sampled at 2048 Hz through an external analog-to-digital (A/D) converter
167 (EMG-Quattrocento, OT Bioelettronica, Turin, Italy). The force signal was recorded with the software
168 OTbiolab (OT Bioelettronica, Turin, Italy) and a custom program written in Labvew 8.0 (National
169 Instruments, Austin, USA) provided the visual feedback.

170 *HDsEMG recordings*

171 A semi-disposal adhesive grid of 64 equally spaced electrodes (13x5 row x columns; gold-coated; 1-mm
172 diameter; 8-mm inter-electrode distance; OT Bioelettronica, Turin, Italy) was placed proximally over the
173 belly of the tibialis anterior muscle of the dominant leg following skin preparation that included shaving,
174 gentle skin abrasion and cleansing with 70% ethyl alcohol. The optimal position and orientation of the
175 electrode grid were determined through palpation and the perimeter of the muscle was marked with a
176 surgical pen (42). Conductive paste was inserted into the bi-adhesive perforated foam layer (Spes
177 Medica, Genova, Italy) in order to enhance the skin-electrode contact. A ground electrode was positioned
178 on the styloid process of the ulna of the arm, and two reference electrodes were placed on the tuberositas
179 tibialis and on the medial malleolus of the dominant leg. The HDsEMG signals were recorded in
180 monopolar mode with a sampling frequency of 2048 Hz, amplified (x 150) and band-pass filtered (10-500
181 Hz). The analog signals were converted to digital data by a multichannel amplifier with a 16-bit resolution

(3-dB bandwidth, 10-500 Hz; EMG-Quattrocento, OT Bioelettronica, Turin, Italy). The electromyogram and force signal were synchronized by the same acquisition system.

HDsEMG analysis

Offline analysis involved band-pass filtering of the monopolar EMG signals at 20-500 Hz (Butterworth). The HDsEMG signals were then decomposed into individual motor unit action potentials (MUAPs) by convolutive blind source separation (22). This method and similar approaches have previously shown consistent identification of motor units for a broad range of forces of the tibialis anterior muscle (21, 33, 43, 45, 47). The pulse-to-noise ratio was used to assess the accuracy of the decomposition (21). The spike trains for the identified motor unit were successively manually analyzed by an experienced investigator and only MUAPs with a discharge pattern that was characterized by a high pulse to noise ratio (>30dB) and visually discernible two-dimensional action potentials following spike-triggered averaging were considered for the analysis (46, 47). We have previously validated and proposed a novel method for robust identification of motor neurons during fast movements (47). Briefly, we spike triggered averaged the HDsEMG using the identified discharge times of each motor unit during the early phase of the isometric rapid contractions (first 20 motor unit discharge times) and compared the extracted motor unit action action potential waveforms with those obtained in the same way during the plateau of force. The two-dimensional cross-correlation assessed the similarity of the action potentials obtained in these two intervals of the contraction. Since decomposition during the steady force phase has been previously validated (47), the similarity across these two phases indicated consistent identification of the action potentials across the early phase of rapid contractions. The other accuracy tests for HDsEMG decomposition during rapid contractions are described in (47). The three contractions that showed the highest peak in force at 150 ms were selected for the final analysis (44).

From the identified motor units, the recruitment threshold in %MVC, and the cumulative spike trains (48) were calculated. The speed of recruitment was defined as the inverse of the time span of recruitment (47). This definition of speed of recruitment only relates to the sample of identified motor units and not to all recruited units.

208 The neural drive to the muscle is the ensemble of axonal action potentials discharged by the motor
209 neuron pool and therefore represents the strength of neural activation. Various signals indirectly
210 associated to the neural drive can be extracted from the decomposed motor unit action potential trains.
211 Since the number of decomposed motor units varied among subjects and was in all cases substantially
212 smaller than the number of recruited motor units, we estimated the average number of motor unit action
213 potentials discharged per motor unit per unit time (pps) across the sample of identified motor units. This
214 measure represents the average discharge rate across the sample of identified motor units. The average
215 discharge rate across the identified motor units was estimated in intervals of 100-ms duration, starting
216 from the onset of motor unit activity up to 1 s following the onset of activity, with 5-ms increments.

217 The estimated correlation between spike trains was computed from the same time intervals as the
218 average discharge rate. Before computing the cross correlation, the cumulative spike trains were filtered
219 by a moving-average filter with Hanning window of 25-ms duration, which corresponds to a bandwidth of
220 ~40Hz. The discrete-time series of filtered spike trains were then grouped and cross-correlated across
221 random permutations of the motor units selected in each group. The cross-correlation was computed for
222 groups of motor units of increasing size. The size of the motor unit groups was progressively increased,
223 starting from a pair of motor units (i.e., two motor unit spike trains). For example, when the decomposition
224 identified 8 motor units, the synchronization was estimated by cross-correlation of cumulative spikes
225 trains from groups of 1, 2, 3, and 4 motor units, and in each group the selected motor units were
226 permutated from the detected motor units. From the cross-correlation analysis, we then estimated metrics
227 to describe motor unit synchronization, as follows:

228 • The proportion of common synaptic input (δCSI) corresponded to the derivative of the sequence
229 of cross-correlation values as function of the number of motor units used for computing the
230 cumulative spike trains in the two cross-correlated groups. For this analysis, a maximum of 8
231 motor units was used (i.e., groups of 4 motor units). The δCSI is an estimate of the rate of
232 increase in cross-correlation when increasing the number of motor units and therefore is indirectly
233 associated to the relative proportion of common input with respect to independent input (34).

- The cross-correlation value ($Synchronization_i$) between groups of 4 motor units as computed in the first 100 ms of contraction.
- and the cross-correlation value ($Synchronization_p$) computed from groups of 4 motor units in an interval of 100 ms during the force plateau phase of the rapid isometric contraction.
- The average cross correlation (after permutation) value of two randomly selected motor unit pairs ($Synchronization_2$).
- The maximal cross-correlation value during the entire contraction ($Synchronization_{MAX}$) computed from groups of 4 motor units.

Force signal analysis

The force signal was converted to Newton (N) and the offset of force was gravity corrected. We then removed the contractions that showed pre-tension or countermovement, which was assessed as changes in baseline force ≥ 0.5 N within the 150 ms prior to force onset. A zero-lag low-pass filter with cut-off frequency 400 Hz was applied to the whole length of the force signal. This large bandwidth is necessary for high accuracy when visually determining the force onset (41, 44, 47). The onset of force was visually identified by an experienced investigator using criteria that were previously described (40). After onset identification, the force signal was low-pass filtered with a 20 Hz zero-lag 3rd order Butterworth filter since this type of filter eliminates the high-frequency noise of the load cell and guarantees an undistorted force output in comparison to the original signal (44, 47). We then selected the three contractions with the highest force at 150 ms from force onset and measured the rate of force development. The force signal was analyzed in the 250-ms interval following force onset. The maximal rate of force development corresponded to the first derivative of force in consecutive time intervals of 1 ms, starting from force onset (i.e. rate of force development 0(onset) to X ms, where X varied in the range 1-250 ms). The peak rate of force development 0-X was used for the correlation analysis described below.

Statistical analysis

The Shapiro-Wilk test was used to assess the normal distribution of the data and the assumption of sphericity was verified by the Mauchly's test and the Greenhouse-Geisser correction was applied when the assumption was violated. Bivariate correlations in the simulation and experimental data were assessed by computing the Pearson product-moment correlation coefficient. Moreover, multiple correlation analysis was used to assess the prediction power of the independent variables on the rate of force development. The amount of synchrony in the motor unit discharge time instants (spike correlation) was assessed by computing the cross-correlation function in time intervals of 60 and 100 ms across the identified motor unit pool, after convolution (see Methods). All statistical analyses were performed using MATLAB 2018b (MathWorks, Natick, USA) and significance was accepted if the P-value was < 0.05. Results are reported as mean ± standard deviation (SD) in the text.

RESULTS

Simulations

The estimated correlation between motor unit spike trains is influenced by the number of action potentials and therefore by the strength of the neural drive to the muscle. Any experimental associations of motor unit synchronization (spike correlation) and rate of force development might be the result of changes in the discharge rate of motor neurons rather than an increase in the proportion of common synaptic input to motor neurons. This hypothesis was tested by the simulation model since it could not be directly analysed experimentally.

When the strengths of synaptic currents increased, we consistently observed an increase in motor neuron discharge rates that was associated with a faster rise in muscular force ($R>0.7$, $P<0.0001$, Fig. 1B,D). We then varied the relative proportion of common vs independent input (Fig. 1C,E) in the range 50%-100% and we did not observe any effects on the rate of force development (Fig. 1C,E $P<0.05$). Therefore, the relative strength of common input, which is one determinant of motor unit synchronization, did not influence the rate of force development. We then fixed the relative strength of common input to motor neurons but increased the strengths of synaptic currents, thus increasing the absolute common input. The

increase in synaptic input consistently increased the estimates of correlation between discharge times, albeit the relative proportion of common input was constant (Fig. 1F, $R>0.7$, $P<0.0001$). These results indicate that the strength of common input to motor neurons relative to independent input does not determine the maximal rate of force development of a muscle and that the main determinant of rate of force development is motor unit discharge rate. Moreover, these results collectively suggest that the estimates of correlation between motor unit spike trains are strongly influenced by the motor neuron discharge rates (determined by synaptic currents) and are thus not strongly associated to the relative proportion of common input.

The absolute correlation values obtained from the cross-correlogram analysis tended to be very close to the maximum ($R =\sim1$) when using the full motor unit population in the model (Figure 1). Conversely, when a limited number of motor unit was considered (<8 motor units), the correlation was lower ($R < 0.8$). It was therefore expected to observe lower correlation values from the experimental data since a relatively small number of motor units, with respect to the entire population, could be identified by decomposition.

Experiment

Motor unit decomposition

Figure 2A shows an example of the motor unit action potentials recorded by the HDsEMG grid. Each color in Figure 2B corresponds to the discharge times of an individual motor unit that was identified across the three contractions. From the discharge times, identified by blind source separation techniques, the validity of the decomposition was further verified by comparing the 2D cross correlation of the motor unit action potentials extracted by spike triggered averaging. An example of a motor unit action potential plotted as a function of amplitude and location over the muscle is shown in Figure 2C. The accuracy and validity of EMG decomposition in the conditions of this study was previously assessed (47). All motor units had a pulse-to-noise ratio >30dB and a 2D cross-correlation value >0.8. The total number of motor units identified per subject was on average of 12.1 (5.7) ranging from 4 to 25 motor units.

Spike correlation analysis

The correlation between motor units was assessed by computing the cross-correlogram of the discharge times of the identified motor unit population (Fig. 3). Figure 3A shows an example of 21 motor units that were decomposed from one representative rapid contraction and the associated cross-correlogram (Fig. 3B). The spike correlation increased when increasing the number of motor units in the cumulative spike trains. The rate of change in the correlation strength between motor unit discharge trains is an estimate of the proportion of common with respect to independent synaptic input, as previously shown (34). Indeed, in this study we consistently observed an increase in the estimated proportion of common synaptic input when adding pairs of motor units in the cumulative spike trains (Fig.3). From this relationship we calculated the correlation value obtained with 8 motor units and the derivative of the increase in the proportion of common input (see section on correlation). For the analyses that included the proportion of the common input, we removed the subjects with a number of motor units lower than 8, giving a total sample of 16 subjects. We chose 8 motor units as a threshold because a lower number may bias correlation analysis towards the independent input to motor neurons (34).

Because the average motor unit discharge rate and the cross-correlation of the motor unit spike trains was estimated in consecutive time windows, it was possible to compute the bivariate correlation between the average discharge rate and motor unit synchronization at the individual subject level. Figure 4 shows representative examples from three subjects, showing strong correlations between the average discharge rate (which estimates the strength of neural drive in the experimental data) and estimated motor unit synchronization. For all subjects, the level of correlation was similarly high ($R>0.75$, $P<0.0001$). This association indicates the influence of discharge rate on the cross-correlation of motor unit spike trains, as shown in the simulations.

As previously mentioned, the association in Figure 4 varies across subjects. Thus, the absolute influence of the number of identified motor units on the correlation between motor unit spike times cannot be predicted. We therefore associated the number of identified motor units to motor unit synchronization at the population level (Fig.5). Each color in Figure 5 represents one subject. Figure 5A represents the motor unit synchronization in the early phase (first ~100 ms) and Fig. 5B corresponds to the plateau

phase of the rapid force contraction. The increase in number of motor units corresponded to an increase in the strength of correlation ($R>0.88$, $P<0.0001$, Fig. 5), as predicted by the model.

Spike correlation, discharge rate, and rate of force development

We performed bivariate and multiple regressions on the extracted neural variables and rate of force development. Figure 6 shows the bivariate analysis for some of the spike correlation indexes and rate of force development. The amount of synchronization (correlation between spike trains) was associated to the rate of force development. However, when these variables were analysed with a multiple regression model, the average discharge rate predicted most of the variance in rate of force development (60%, $R=0.78$, $P<0.001$). On the other hand, the indexes of motor unit synchronization explained <40% of the variance with P values <0.01, and some non-significant ($P>0.05$) (the average coefficient of correlation R was 0.36 (0.20), ranging from 0.14 to 0.53). Moreover, the association between correlation of spike trains and rate of force development was determined by the influence of discharge rate on the correlation level (Fig. 6F). Indeed, the average discharge rate predicted the changes in motor unit synchronization across subjects and recruitment speed predicted motor unit synchronization (Fig.7).

Figure 8 shows the time course of motor unit synchronization when analyzed in different time intervals from the onset of the first detected motor unit action potential for all subjects. The synchronization level was maximum at the onset of the contraction and decreased until reaching a plateau (Figure 8; Paired-test $P<0.001$). The time-course of motor unit synchronization (Fig 8.B) matched the changes in discharge rate that were previously observed (47).

DISCUSSION

This work shows that the relative strength of common versus independent synaptic input to motor neurons does not influence the maximal rate of force development produced during rapid ankle dorsiflexion. Although the initial phase of the rise in muscular force showed a higher motor unit synchronization and was correlated with the rate of force development, these findings were attributed to the increase in discharge rate of motor neurons. This study also demonstrated that during single-joint

actions the only determinant of rate of force development across individuals is the neural drive to the muscle as determined by motor neuron recruitment speed and discharge rates.

Common synaptic input to motor neurons

Motor neurons receive common and independent synaptic inputs from spinal and supraspinal circuitries. The common inputs largely influence the force fluctuations. For example, during a steady isometric contraction, the low frequency component of the motor unit discharge rates predicts most of the variance in force (32, 48). Because of the presence of a proportion of common input, the correlation between spike trains of groups of motor units tends to the maximum value of 1 when increasing the number of motor units (11). Indeed, the output of groups of motor neurons is an average of their spike trains that enhances the common with respect to the independent components (11).

It has been generally assumed that synchronous discharges of motor units would positively impact the rate of force development of a muscle (2, 23, 29, 38, 39). However, during very fast voluntary movements, most motor units are recruited in less than 60 ms and discharge at high rates (>100 Hz) (47). The high discharge rate coupled with fast recruitment, generates spike correlations that are ~1 (Fig 1,5). We verified this hypothesis with experimental findings and with a motor unit model that confirmed strong correlations between the strength of the synaptic input and speed of force production. Conversely, the relative proportion of common versus independent inputs to the motor neurons was not associated to the rate of force development. Moreover, the significant correlation between motor unit synchronization and rate of force development was explained by the influence of discharge rate in both measures (Fig. 1).

The numerical simulations were then confirmed with experimental data obtained from the human tibialis anterior muscle during contractions at maximal rate of force development. The increase in discharge rate modulated the synchronization of the motor units in an input-dependent way (Figs. 3-5). The significant associations between the spike correlations and rate of force development were a byproduct of the influence of discharge rate on both measures (Figs. 3-8), as it was concluded from the modeling analysis. The determinants of rate of force development are therefore either the high synaptic inputs from the cortex and/or the intrinsic properties of the motor neurons.

Functional significance of common synaptic input during fast movements

The functional significance of synchronization during dynamic movements is unclear. A certain degree of common input across motor neurons is a needed neural strategy for controlling muscle force (14, 25), therefore the discharge times of motor neurons inevitably show correlation. The correlation level depends on many factors in addition to the relative strength of common input, including the motor unit discharge rates and the intrinsic motor neuron properties (24).

Motor unit models show that the peak rate of force development in single motor units is mainly determined by their discharge rates (10). Here we show that a pool of motor neurons can produce the same rate of force development within a wide range of relative strengths of common synaptic inputs (Figure 1). The determinants of rate of force development therefore relies on the synaptic drive to the motor neuron pool and intrinsic motor neuron properties. The number of recruited motor units during fast contractions is an indirect measure of how fast upper motor neurons are recruited by cortical circuitries. We indeed found strong correlations between the motor unit recruitment speed and rate of force development.

Conclusions

It has been previously speculated that motor unit synchronization plays a role in the rate of force production. However, this assumption was not verified in the present study. Coversely, we provide evidence that the relative proportion of common synaptic input sent to the motor neuron pool is not a determinant of the rate of force production. The common input determines correlation among spike times which is also strongly influenced by the discharge rate. The main determinant of rate of force development is determined by the speed of recruitment and the average discharge rate of the recruited motor units and not by the degree of correlation of their discharges.

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Figure Captions

Figure 1. **A**. Input and output parameters of the motor unit model. A pool of 188 motor neurons received a range of synaptic currents (SC) plus an independent noise to each cell reflecting its unique connections and a common input that ranged within the boundaries of the physiological range of the motor unit interspike intervals. The motor unit force was modelled with previous described equations (18). Briefly, the total force $F_{TOT}(t) = \sum_{i=1}^{n} F_i(t)$ represents the sum of the force profile of each motor unit F_i that is

defined by $F_i\,(t) = \sum_{i=1}^{n} f_{ij}\,(t - t_{ij})$, where $f_{ij}\,(t - t_{ij})$ represents the force of each motor unit given by the discharges of motor neuron j. **B**. The discharge times of the population of motor neurons during the first 100 ms of a simulated rapid contraction. In the first example (**C**) the common synaptic input to motor neurons was fixed at a constant value (~50% of maximum) and the synaptic input was progressively increased to give a range of discharges that decreased exponentially within the ~40 Hz range (47). The lower the synaptic input (grey lines) corresponded to lower rate of force generation. The increase in the synaptic input consistently increased the rate of force development (black lines). When the synaptic currents were fixed at a constant value (50% of maximum, ~100 Hz) and the common synaptic input was progressively increased we observed no changes in the force-time curve (**c**). **D.** Association between the average number of discharges of the motor unit pool per second (pps) and the peak of the rate of force development (RFD, N/s). **E.** Common synaptic input strength (%, see Methods) as a function of rate of force development. In this example, the synaptic input was fixed at 50% of maximal synaptic input (see A-C). **F.** The synaptic currents were modulated as in **D** and the correlation strength between motor unit spike trains (motor unit synchronization) was computed via the cross-correlation function. Although the common input strength was constant (50% of maximum), motor unit synchronization was positively associated with rate of force development. This association implies that changes in motor unit synchronization are strongly modulated by the increase in the discharge rate of motor neurons and that the common synaptic input to motor neurons is not a determinant of rate of force development. Each data point in D-F corresponds to a simulated rapid contraction and the header shows the coefficient of correlation (R) and Pearson P value.

Figure 2. **A.** The motor unit and its three-dimensional action potential recorded by a HDsEMG grid after decomposition. **B.** Discharge times of seventeen motor units identified by surface EMG decomposition during three rapid muscular contractions (black lines) for one representative subject. **C.** The motor unit action potential extracted by spike triggered averaging was plotted in a three-dimensional space that corresponds to the amplitude and location over the muscle (columns and rows of the HDsEMG grids). The spike triggered average for same motor unit is shown across the three contractions. Note that the 3D spike triggered action potential corresponds to an individual value in the bidimensional array (which was centered in the middle of the action potential).

564

565 Figure 3. **A.** Raster plot of the motor unit spike trains during an isometric rapid muscular contraction. **B.**
566 Cross-correlation function in 100 ms time windows with a 5 ms overlap. Each line represents the cross-
567 correlogram obtained in a time window. The spike trains in B were randomly divided in two groups and
568 convolved with a 25 ms Hanning window. The ordinate represents the absolute motor unit
569 synchronization value across the identified motor unit pool **C.** Proportion of common synaptic input as a
570 function of the number of motor units used to calculate the cross-correlation. Each color corresponds to
571 the data from an individual subject. The inset in C shows the average value with the standard deviation
572 across the three rapid contractions for three representative subjects. Note the increase in the proportion
573 of synaptic input which indicates the averaging process achieved by the population of motor neurons with
574 respect to the independent input that each cell receives.

575 Figure 4. Correlation between motor unit synchronization and average discharge rate for three
576 representative subjects (**A-C**). Each point on the x-axis corresponds to the average number of discharges
577 per motor unit per second (average discharge rate, pps) during a rapid isometric contraction. The
578 synchronization corresponds to the average cross-correlation function between 100 permutations of the
579 cumulative motor unit spike trains. The average discharge rate and motor unit synchronization were
580 processed in 100 ms time intervals and with 5 ms overlap. Note the linear relationship between these two
581 variables indicating the high influence of discharge rate on motor unit synchronization. The header shows
582 the correlation coefficients (R) and Pearson P-values.

583 Figure 5. **A.** Association between the average number of action potentials during the early phase of rapid
584 force (motor unit count, first 100 ms) and the initial value of $Synchronization_i$ for the first 100 ms at the
585 individual subject level (each data point represents a subject, n = 20) **B.** The same as in A but during the
586 plateau phase of the rapid force contraction. The associations in A and B show that the value of
587 synchronization is largely influenced by the number of motor units that are used for the computation of the
588 cross-correlation function, and that the correlation strength tends to ~1 when large populations of motor
589 units are identified (n = 20). The header shows the correlation coefficients (R) and Pearson P-values.

590 Figure 6. Associations between several neural parameters extracted from the motor unit spike trains and
591 maximal rate of force development (RFD_{MAX}). Each color represents one subject (total number of subjects
592 in each panel = 16). **A**. The cross-correlation strength of the motor unit spike trains for the first 100 ms of
593 rapid force ($Synchronization_i$), and during the plateau phase of the contraction (**B,** $Synchronizaiton_p$). **C.**
594 The derivative (δ) of the proportion of common synaptic input to motor neurons (δpCSI, see Methods)
595 normalized to the number of active motor units as a function of RFD_{MAX}. The δpCSI corresponds to the
596 increase in common synaptic input by the motor unit population. **D.** The initial value of synchronization for
597 pairs of motor units ($Synchronization_2$) vs. RFD_{MAX}. **E.** Maximal value of synchronization
598 ($Synchronization_{MAX}$) across subjects and the average discharge rate. **F.** Association between RFD_{MAX}
599 and the average discharge rate. The header shows the correlation coefficients (R) and Pearson P-values.

600 Figure 7. Association between motor unit recruitment speed (Motor unit/s) and synchronization for the first
601 100 ms (**A**, $Synchronization_i$) and at the plateau of the rapid force (**B**, $Synchronization_p$). The motor unit
602 recruitment speed is the derivative of the intervals of activation of the identified motor units. The header
603 shows the correlation coefficients (R) and Pearson P-values (number of subjects = 16).

604 Figure 8. Average value for the rapid isometric ankle-dorsiflexion contractions (**A**) and for the peak of the
605 cross-correlogram, which provided a measure of motor unit synchronization (**B**) across all subjects. The
606 error bars represent the standard deviation across subjects. The average value for both force and
607 synchronization was obtained in 100 ms time windows with 5 ms overlap. The dashed lines correspond to
608 the initial value (first 100 ms) and the value that was averaged at the plateau phase of the contraction.
609 The lower panel (**C**) shows the box plot across all subjects for the initial and plateau value of the motor
610 unit spike times correlation strength.