
**Population Coding of Neural
Drive in Human Motor
Units during Voluntary
Isometric Contractions**

Population Coding of Neural Drive in Human Motor Units during Voluntary Isometric Contractions

PhD Thesis by

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ABSTRACT

The execution of a movement is the result of a complex interaction between populations of neurons in the central nervous system. Nowadays, we have a detailed knowledge of the mechanisms of functioning of single neurons *in vitro*, but we lack a broader view of the network connections. The identification of the physiological mechanisms that are responsible, at the macro level, for the generation of movements is important to understand how to reestablish damaged pathways. This PhD thesis focuses on the analysis of populations of motor units *in vivo* in humans to extract information about the synaptic control signals involved in the production of isometric movements. Moreover, it investigates the limitations of the current techniques for the estimation of the neural drive to the muscles. The first study (STUDY I) investigated the possibilities of separating the contributions of individual motor units from the surface electromyographic (EMG) signal. The work demonstrated that the use of multichannel electrodes can effectively improve the detection of populations of motor units from the surface EMG. Therefore, the second study (STUDY II) used a combination of surface and intramuscular EMG electrodes to increase the motor unit sample size for the investigation of the low-frequency neural signals to the muscles during isometric contractions. The results demonstrated that a low-dimensional control signal can be extracted by the concurrent observation of a relatively large pool of motor unit spike trains. This low-dimensional signal is the effective drive to the muscle since it is directly translated into force, as demonstrated experimentally in STUDY I. Three additional studies clarified the relation between the neural drive to muscles and cortical oscillations. STUDY III investigated the variability in the estimation of the corticomuscular coherence, a common technique for assessing supraspinal control, when EMG signals from several locations over the muscle are used. Since the results demonstrated strong limitations of this technique, STUDY IV focused on estimating the corticomuscular coherence directly from the spike trains of motor units and analyzing the transmission of cortical oscillations to the motoneuron pool. It was shown that the central nervous system can transmit

cortical oscillations to the motoneuron pool in a partly linear way by projecting common input to the entire motoneuron population. Despite linear transmission is achieved in this way, it is unclear if linear methods concurrently analyzing EEG and EMG can reveal it in a robust way, a topic that was investigated in the last study of the thesis. STUDY V used a realistic computational model of populations of motoneurons to identify factors of influence in EMG/EEG coherence analysis. The results showed that the interaction of common synaptic activities from muscle afferents and supraspinal centers on the motor neuron pool may influence each other and underestimate the real corticospinal interactions.

ABSTRAKT

Bevægelse er et resultat af et komplekst samspil imellem populationer af nervefibre i det centrale nervesystem. I dag, har vi et detaljeret kendskab til virkemåden af enkelte nerve fibre in vitro, men vi mangler det store overblik over hvordan disse nerve fibre skaber funktionelle netværk i nervesystemet. Identifikationen af de fysiologiske mekanismer på det makroskopiske niveau som er ansvarlige for udførelsen af bevægelser er nødvendigt før vi vil være istand til at genetablere ødelagte forbindelser i nervesystemet.

Denne PhD afhandling omhandler en analyse af motor enheder in vivo i mennesker for at få informationer om de synaptiske kontrol signaler som er involveret i produktionen af isometriske bevægelser. Derudover omhandler den et studie af de nuværende teknikker for estimation af den neurale kontrol af musklerne.

Det første studie (STUDIE I) undersøgte mulighederne for at seperere bidraget fra individuelle motor enheder optaget med det overflade electromyografiske signal. Dette arbejder demonstrerede at brugen af flere elektroder kan effektivt forbedre optagelser af populationer af motriske enheder. Dette afledte det andet studie (STUDIE II) som brugte en kombination af intra- og overflade elektroder til at maksimere antallet af studerede motoriske enheder som blev studeret under isometriske kontraktioner. Resultaterne deminstrerede at et low-dimensionalt kontrol signal kan findes fra samtidige observationer af en stor gruppe motoriske enheder. Dette kontrol signal er det effektive kontrol signal til musklen siden der er en direkte sammenhæng imellem størrelsen af dette signal og den genererede kraft fra musklen (STUDIE I). Tre yderligere studier undersøgte yderligere denne relationen imellem kontrol signaler og de kortikale oscileringer. STUDIE III undersøgte variabilitetet i estimering af cortico-muscular coherence baseret på EMG fra flere lokalitioner over muskel. Cortico-muscular coherence er en teknik til at estimere den supra-spinale kontrol. Siden resultaterne demonstrerede store mangler med denne teknik blev der udført en fjerede studie (STUDIE IV) som fokuserede på at estimere cortico-muscular coherence direkte fra signalet fra enkelte motor enheder og

analysere transmissionen af cortikale oscilleringer til gruppen af motor neuroner i en muskel. Det blev vist at centralnervesystemet transmittere disse cortikale oscileringer i en delvis lineær vej til hele populationen af motor enheder. På trods af virkemåden af denne transmission er det uklart om linear analyse metoder kan benyttes i EEG og EMG til at undersøge emnet for dette studie. STUDIE V brugte en realistisk beregnet coherence analyse, og viste at interaktionen imellem fælles synaptiske aktiviterer fra afferente nervefibre i musklen og supra-spinale centre som kontrollere de motoriske enheder kan påvirke hinanden og underestimere de reelle kortiko-spinale interaktioner.

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CHAPTER I

Introduction

“You're nothing but a pack of neurons”.

Francis Crick

In everyday life, it is general opinion that “many are better than few”. The idea comes from the fact that a multitude of individuals (well coordinated) has usually a stronger (and often better) impact on the environment compared with a smaller group (Aristotle, *Politics*). The statement is clearly valid at the macroscopic level, for example talking about insects, animals or humans, but it has even more importance at the microscopic level. Biological systems are probably those where this idea is pushed at the limit, since it is quite simple to find examples of ensembles of simple cells that can perform incredibly complex achievements. Within the biological structures, the central nervous system of primates and humans is probably the most elaborate (and impenetrable) entity ever built by nature.

Mammalian central nervous system is constituted by a large amount of different types of neurons. Each type of neuron has several individual characteristics that are optimized for the corresponding region or area that they belong to (Kandel et al., 2000). However, a typical neuron has a rather simple structure and its input-output transfer function can be reduced to a threshold integrator with a variable gain (Gerstner & Kistler, 2000). Its main purpose is to sample the incoming information and retransmit it with amplification. In these terms, an isolated neuron has limited capacity to encode complex behaviors. Nevertheless, when several neurons interact together the range of possible output actions can increase dramatically. Populations of neurons could encode quite complex behaviors and show high levels of adaptation in their characteristics.

The importance of population integration was first demonstrated by Hebb (1949) and confirmed by thousand of studies later on (see for a review, Averbeck et al. 2006).

The interaction between populations of neurons is critically important in the part of the central nervous system involved in the control of movements. Large groups of motor neurons in the motor cortex cooperate with motor neurons at the spinal level in order to perform skilled combinations of movements (Kandel et al., 2000). The basic principles of this process are well known, but the full understanding of it is still an open problem. Without that, rehabilitation therapies and technologies are destined to proceed by trial and error, in the darkness.

The aim of this work is to give new insights in the understanding of the central drive to muscles in humans. In particular, it will focus on the information extracted from the behavior of populations of motor units *in vivo* during isometric contractions.

CHAPTER II

Principles of movement control

This chapter describes the basic physiology of muscle contraction. It follows a backward description, starting from muscle fibers and the generation of the EMG signal, going through the organization of the spinal cord and ending with the cortical projections from the motor cortex. The description follows approximately the path taken in the studies described in the thesis.

Physiology of the muscle contraction

In humans, the motor system can produce very precise and powerful movements, depending on the environmental demands. Any action usually requires the concurrent activation of several muscles with a precise tuning of the force generated by each muscle. A single muscle is constituted by many muscle fibers that are responsible for the generation of force. Instead of controlling each fiber individually or on a whole, the muscle is divided in many subsections, called muscle units (Heckman & Enoka, 2004). Each unit represents the mechanical transducer of one motoneuron. The ensemble of a motoneuron, its axon and the muscle unit that the axon innervates is called motor unit (Enoka, 2000). Muscle fibers differ for composition, and they can be divided in two main groups, fatigable and not fatigable muscle fibers. Muscle units are also ordered by size (number of muscle fibers) and a kind of correspondence between dimension of the muscle units and fatigability exists, with the smallest units being more resistant (but generating less force) to fatigue than bigger ones (that generate also more force) (Burke et al., 1973). The total number of muscle fibers and muscle units is variable and related to the performance each muscle has to achieve (e.g. Buchthal 1961; Santo Neto 1961).

The muscle fibers generate force through a sliding process of two filaments (actin and myosin), elicited by the action potentials arriving from the axon of the motoneurons (Kandel et al., 2000). Therefore all the muscle fiber of a given muscle unit will contract together and one-to-one relation exists between the action

potential elicited by the motoneuron and the twitch force generated by the corresponding muscle unit (Heckman & Enoka, 2004).

During voluntary contraction, each muscle fiber generates an amount of contractile force and electrical activity that propagates across the entire length of the muscle. An electrode placed in the muscle belly or on the surface can record the electrical activity of the muscle fibers in its proximity (Farina et al., 2010). The recorded signal is called electromyographic signal, or EMG.

The motoneuron pool and the organization in the spinal cord

In the motor unit, the controller is the motoneuron. It integrates all the neural inputs that synapse on its dendrites and, through rate coding, controls the muscle unit to produce the required level of force (Heckman & Enoka, 2004). The motoneurons are ordered by size, with the smallest activated by the least current compared with the bigger ones. Once a motoneuron is recruited, changes in the synaptic input and in its intrinsic properties (Heckman et al., 2008) are reflected in the frequency of the generation of action potentials. This results in a simple way to control the total force generated by a muscle, giving the possibility to perform fine movements as well as powerful ones.

There are several types of synaptic inputs that reach the motoneurons for controlling the force production (Gandevia, 2001). Most of them are highly spread across all motoneurons, or the motoneuron pool, although some are predominant over motor neurons associated with particular types of fiber (Heckman & Enoka, 2004). Many projections on the motoneurons that are arising at the spinal level originate from sensory fibers. The most important during muscle contractions are type Ia (excitatory) and Ib (inhibitory) (Heckman & Enoka, 2004). The distribution and characteristics of those synaptic inputs are mainly unknown. An exception is given for the Ia muscle spindle afferents that are known to have monosynaptic connections (no interneurons involved) highly spread over the entire motoneuron pool (Kandel et al., 2000).

Corticospinal pathways and the motor cortex

A large part of the synaptic inputs to the motoneuron pool originate at the supraspinal level and it is related with the volitional motor commands (Kandel et al. 2000). Those inputs can be divided into projections from the brainstem and from the motor cortex. The former are known to be responsible for the generation of postural adjustments during locomotion and are evolutionally relatively old (Riddle & Baker, 2010). On the contrary, the corticospinal projections from the motor cortex are the main direct inputs of the human motor system and are believed to be involved in the generation of fine movements, in particular of the upper limbs (Lemon 2008). They project to several motoneuron pools (Buys et al., 1986) controlling the activation of the muscles by groups, instead of individually. Recently, using a retrograde viral tracing technique, it has been demonstrated that those projections are, at least partly, monosynaptic on the spinal motoneuron pool in primates (Rathelot & Strick, 2006; Lemon, 2008).

CHAPTER III

State-of-the-art in the identification of the neural drive to the muscle

This chapter describes the methods that are currently used to gather information about the neural drive to muscles during voluntary movements. It explains the techniques and the limitations in their use, in particular to those that lead to the studies illustrated in the thesis.

Inferences from surface EMG

The most commonly used technique for the extraction of the neural drive to muscles is the analysis of the surface EMG (Merletti & Parker, 2004). The information extracted by the analysis of the surface EMG signal is considered an estimation of the global activity of the active motor units. General features, such as the amplitude in the time and frequency domains, are believed to be related to the actual number and type of motor units active, and therefore to the amount of synaptic drive that the motoneuron pool receives (Merletti & Parker, 2004). Unfortunately, it is incorrect to draw these conclusions from the analysis of the surface EMG. Several factors can influence the generation of the signal, and both central and peripheral factors could interplay in a way such that the separation of the contributions may be a complex problem. For example, during sustained fatiguing contractions, recruitment of new motor units and changes in the intracellular action potential profiles may produce several nonlinearities and disrupt the relation between neural drive and output EMG signal. Moreover, the effects of the volume conductor (e.g., thickness of cutaneous and subcutaneous tissues, distribution of the motor unit territories, inclination of the fibers) can highly influence the properties of the motor unit action potentials recorded on the surface of the muscle (Farina et al., 2004). The volume conductor has also an effect on the possibility of identifying individual motor unit action potentials from the surface EMG. Low-pass filtering effects of the volume conductor may distort the action

potential characteristics and increase the similarity between different motor units. This phenomenon can strongly limit the performance of decomposition algorithms and it is addressed in Chapter VI (Study I). Figure 1 shows an example of mechanical and electrical properties of two motor units, based on a model description (Fuglevand et al. 1993, Farina et al. 2004). Although the two motor units have quite different dimensions (muscle fibers territories) and therefore different muscle twitch forces, their action potentials recorded on a random location over the skin are very similar. This is due to the fact that the two motor units have different positions in the volume conductor, with one much deeper than the other. In these conditions, any inference based on the amplitude of the surface EMG signals generated by those two motor units will lead to wrong conclusions about their properties. Moreover, it is not possible by any decomposition algorithm to resolve two spike trains of those two motor units without more spatial information (Study I).

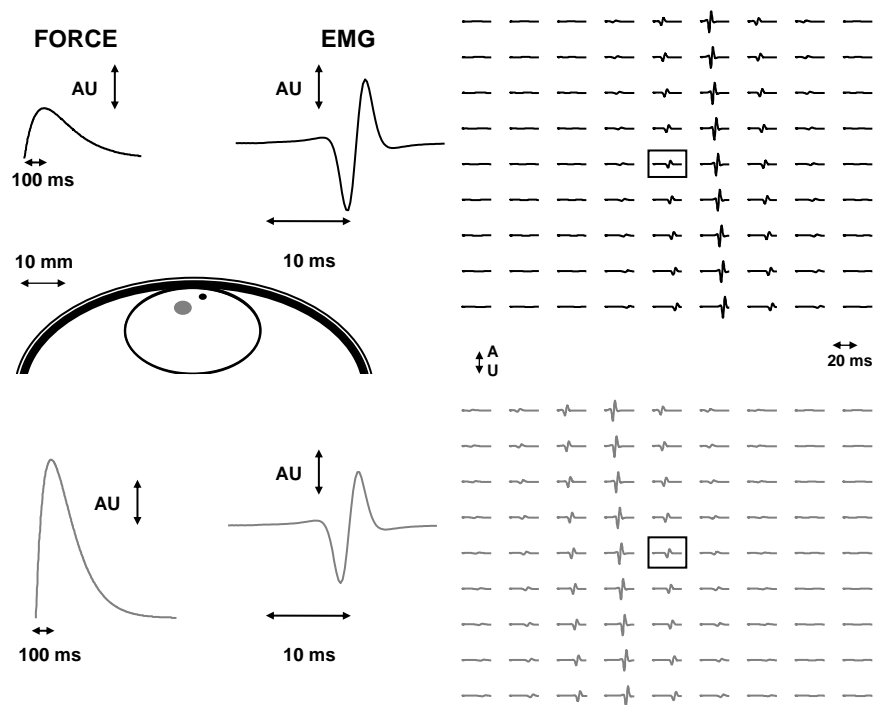


Figure 1. Two motor units with different territories produce a variable amount of force, but can have a similar EMG amplitude if the spatial variability of the amplitudes is not exploited.

Amplitude cancellation, that arises when action potentials in opposition of phase cancel each others, can disrupt the relation between the actual neural activity generated in the spinal cord by the motoneuron pool and the detected electrical potentials on the surface of the muscles (Keenan et al. 2006; Farina et al. 2008). Therefore, the relation between the surface EMG and the generated force is non linear. This problem is partly addressed in Chapter VII (Study II). As for the amplitude, also the spectral characteristics of the surface EMG signal could be a bias estimation of the spectral content of the motor unit activity. The power spectrum of the EMG signal depends on the discharge rates of the active motor units, their firing variability and the spatial location of the recording points across the muscle (Farina et al. 2004). Therefore, using frequency based method applied to the surface EMG for the estimation of the properties of the neural drive to the muscle may be misleading. The problem was partly addressed in Chapter VIII (Study III) of the thesis, with the focus on the estimation of the corticomuscular drive (see below).

Analysis of motor unit spike trains

There is a one-to-one correspondence between the information extracted from the output discharge of motor units and the activity of the motoneurons in the spinal cord. Decomposition of the compound EMG signal generated by the activity of the motor units can be performed on intramuscular (Stalberg et al. 1986) or surface signals (Holobar & Zazula, 2004; DeLuca et al. 2006). Several parameters can be extracted from the spike trains of the motor units. Discharge rate is the number of action potentials generated by a single motoneuron in one second, and it is indicative of the synaptic inputs that the neuron receives plus the modulation of intrinsic properties (Heckman & Enoka, 2004). The variability of the discharges (often measured as standard deviation divided by the mean, aka coefficient of variation CoV) is related to the normalized variability of the synaptic inputs (Calvin & Stevens, 1967, 1968). The variability of the discharge rate of the motor unit is also believed to influence the performance of the motor task (Baudry et al. 2009). Chapter VII clarifies partly this particular topic. The discharge rate and the coefficient of variation are related to the power spectrum characteristics of the spike train. As an example, figure 2 shows the power spectrum

of three spike trains with similar discharge rates, but different coefficients of variation for the inter-spike intervals (inverse of discharge rate). The effect of the changes in the latter is evident and it can dramatically modulate the amplitude of the high frequency harmonics. As mentioned previously, this phenomenon has influence also on the spectral characteristics of the surface EMG signal. Moreover, the power spectrum of the output spike train of a motoneuron also reflects the spectral content of the synaptic input signal. A simplified mathematical derivation of the power spectrum in output of an integrate and fire neuron model can be found in the work of and Bawly (1968) and Nakao (1997). Chapter IX (Study IV) describes the implications of this phenomenon when populations of motoneurons are receiving similar synaptic inputs.

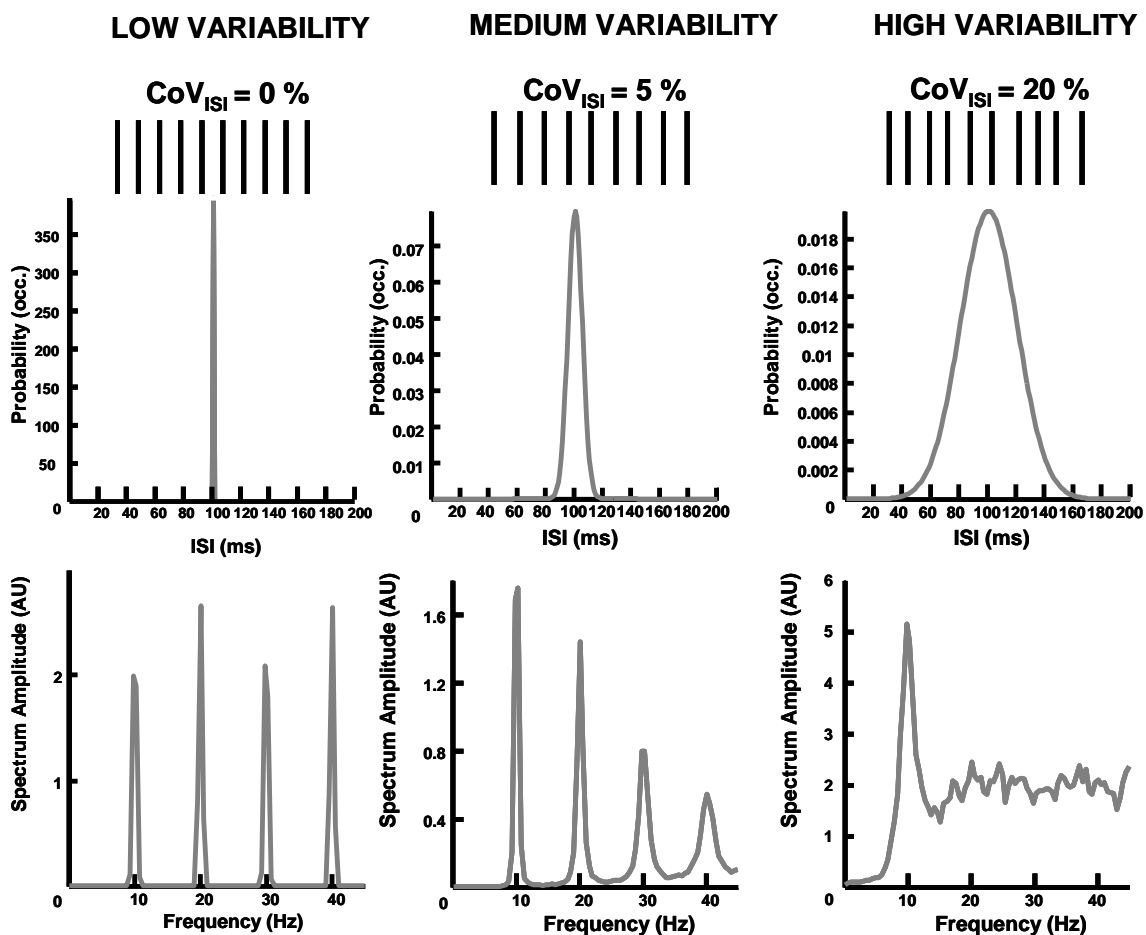


Figure 2. Power Spectra of three spike trains with different variability of inter-spike intervals (ISIs). The effect of the increase in coefficient of variations for ISI is modulating the amplitude of the higher harmonics in the spectra of the spike trains (bottom).

Correlation between neural signals

The analysis of the correlation between neural signals is a widely used method to estimate the amount of inputs that are shared between simultaneously active neural regions (Perkel et al. 1967). For the study of the common activation of different motoneurons, several techniques have been developed, both in time (common drive, short term synchronization) (De Luca et al. 1982; Nordstrom et al. 1992) and frequency (coherence between motor unit spike trains, corticomuscular coherence) (Rosemberg 1989; Conway et al. 1995) domain. In general, all techniques assume that the amount of correlation in the synaptic inputs is proportional to the correlation that can be measured between the output trains of action potentials. This assumption is a simplification that does not hold in most cases (De la Rocha et al. 2007, Tchumatchenko et al. 2010, Negro & Farina, 2010), unless certain conditions are verified.

Common drive

During steady isometric contractions, human motor units have the tendency to produce common oscillations in their average discharge rates. This phenomenon has been termed common drive and it has been observed in a number of studies (De Luca 1982, 1993, 1996; Erim 1999). It has been studied in relation to handedness (Adam 1998; Kamen 1992), different proprioceptive conditions (Garland 1997), exercise (Semmler 1997) and aging (Erim 1999) It is usually quantified using the common drive index (CDI), that is defined as the peak of the cross-correlation between couples of motor unit spike trains filtered using a strong low-pass filter (hann window 400 ms duration). Figure 3 shows an example of common behaviour between several motor units during a weak isometric contraction. Although widely accepted that the common drive has a central origin, it still remains unclear how much muscle spinal interneuron circuits and afferent feedback interactions can influence this phenomenon. Evidence of common drive in ocular (Kamen 1992) demonstrated that Ia spindles and Reshaw inhibition is not necessary for detecting common drive. Finding in the trigeminal motor system and hand muscles showed that also recurrent inhibition is not essential for common drive. Chapter

VII (Study II) describes the generalization of the correlation between average discharge rates in a population of motor units.

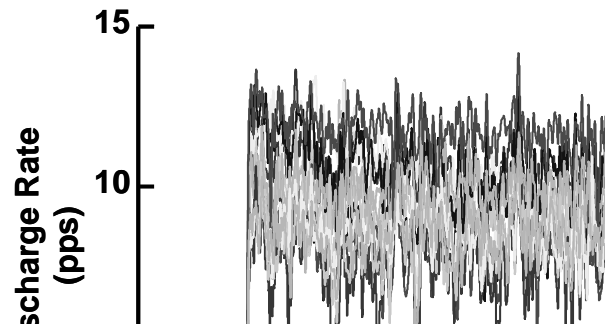


Figure 3. Average discharge rate of several motor units during a sustained isometric contraction. The communality (correlation) between the oscillations of the motor units is evident.

Short-term synchronization

Another measure of correlation between motor unit spike trains is the short-term synchronization (Sears & Stagg, 1976). Several indexes have been proposed (Ellaway & Murthy, 1985; Datta & Stephens, 1990; Nordstrom et al., 1992), but all of them are proportional to the cross-correlation between (unfiltered) motor unit spike trains. The significant level of correlation that is usually found between motor unit spike trains is believed to be related to the correlation induced by the last layer of the synaptic inputs to the motoneurons. The relation between common drive and MU short-term synchronization has also been investigated, but only a weak association has been found (Semmler et al., 1997). Recently, several investigators have focused on studying the parameters that can influence this measure of correlation (Lowery et al., 2007).

Corticomuscular coherence

Recent studies using concomitant recording of EEG and surface EMG have demonstrated significant common oscillations between the electrical activity from the primary motor cortex and muscles. This communality has been proved analyzing the frequency content of the signals and it is confined in the beta

and gamma bands (Mima et al., 1999). The general opinion is that the common oscillation reflects the activity of the descending drive from the CNS to the muscles. This conclusion arises from the observation that EEG and surface EMG are an indirect measure of the cortical and spinal motor-neuron pool activities. Although this deduction is valid from a general view point, there are non-linear processes involved in the generation of the two signals that can lead to wrong interpretations. Common oscillations in the two signals may reflect common drive, although no clear association between corticomuscular rhythms and common drive has been investigated. Corticomuscular oscillations have been found in many studies and their variability assessed during isometric/dynamic contractions (Mima et al., 1999; Kilner et al., 2000), attention/precision tasks (Kristeva-Feige et al., 2001), transcranial magnetic stimulation (Hansen & Nielsen 2004), alteration of proprioceptive condition (Riddle & Baker, 2005), fatigue (Tecchio et al., 2006). All investigations have found consistent oscillations in the beta and gamma band (~20 Hz) but a highly variable strength (Pohja et al. 2005). This variability seriously limits the potentiality of the technique. The limitations are probably due to the statistical weakness of the estimation and the high variability of the frequency content of the two signals during a contraction (see chapter VIII). Moreover, it is not known how much the corticospinal projections are shared across the motoneuron pool. The problem is addressed in chapter IX (Study IV) of this thesis. Another important point is the influence of other common pathways. Spinal motoneuron receive several projections from afferent sensory pathways (see chapter II) that are highly spread over the motor neuron pool. How the oscillations generated by those sensory pathways interact with the cortical ones and influence the estimation of the supraspinal connections is partly addressed in chapter X (Study V).

CHAPTER IV

Aim of the thesis

This chapter describes the main reasons to perform the studies reported in this thesis and the objectives that have been addressed.

The key words of the work are *population coding*. As explained in the previous chapters, the human motor system is based on the interaction between populations of spinal and cortical motoneurons. In order to understand the behavior of the system therefore, it is not sufficient to look at the information extracted from few motoneurons, but some kind of averaging across populations of motoneurons is necessary. According to this view, the present thesis will focus on some problems related with the decoding, connectivity and transmission of information across multiple motor units. In details, the thesis collected the work performed in five scientific studies.

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Detecting the unique representation of motor-unit action potentials in the surface electromyogram.

J Neurophysiol. 2008 Sep;100(3):1223-33, doi: 10.1152/jn.90219.2008.

II) **Negro F., Holobar A., Farina D.** (2009)

Fluctuations in isometric muscle force can be described by one linear projection of low-frequency components of motor unit discharge rates. J Physiol. 2009 587(Pt 24):5925-38, doi:

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Decorrelation of cortical inputs and motoneuron output. *J Neurophysiol.* 2011 doi: 10.1152/jn.00336.2011.

CHAPTER V

General discussions

This chapter presents a general overview of the work described in this PhD thesis. A short description of the aims, methods and results is given for each study. For further details, the reader is suggested to consult the following chapters, where the published research papers or a detailed description of the works are presented.

I. Detecting the unique representation of motor-unit action potentials in the surface electromyogram.

Surface EMG signals provide information about the global activity of several active motor units during muscle contraction (Merletti & Parker, 2004). However, the low-pass effects of the volume conductor interposed between the activated muscle fibers and the recording electrodes can impaired the estimation of the actual neural drive to the muscle. In particular, most of the information in the high-frequency band resulting from the generation of the action potentials is attenuated; therefore the electrical potentials of the motor units have the tendency to look very similar when detected from single electrodes over the surface of the muscle. The phenomenon has important implications for the separation of single motor unit activities from surface EMG (decomposition) (Holobar & Zazula, 2004; DeLuca et al. 2006). The discharges of one motor unit can be uniquely detected only if its electric potentials recorded on the skin are different from that generated by any other motor unit.

In order to investigate this issue, in Study I, we simulated the surface EMG signals generated by populations of motor units and we investigated the relative proportion of uniquely represented motor units using various spatial filters for the surface detection and different volume conductor properties. Briefly, a muscle of elliptical shape consisted of 200 motor units was simulated. The motor units were randomly located in the volume of the muscle and 20 different random distributions were computed. Three locations of the end-plate zone and two fat layers were investigated. After performing the spatial filtering on the simulated surface

action potentials (monopolar, bipolar, double differential, Laplacian and DeLuca (DeLuca et al., 2006) derivations), pairs of motor unit action potentials were analyzed and the ones that differ for more than 5 % of the mean square error were considered identical.

The results suggested that a few surface EMG channels do not allow single motor unit discrimination from the surface EMG. If the number of detection points is increased, the number of individual motor units that is theoretically possible to distinguish is higher. Using the Laplacian spatial derivation with 81 channels, almost all motor units simulated could be discriminated in all conditions analyzed. The results were also validated using recordings on the abductor digiti minimi muscle of eight healthy men. Single motor units discharges were identified from intramuscular EMG electrodes and averaged surface action potentials were derived using the spike trigger averaging technique. As for the simulated signals, the experimental results confirmed that Laplacian derivation and many EMG channels (grid 5 x 5) were necessary for an accurate discrimination of different motor units.

Therefore, multi-channel surface EMG with spatial filtering allows discrimination of individual motor units better than a few set of channels.

II. Fluctuations in isometric muscle force can be described by one linear projection of low-frequency components of motor unit discharge rates.

Descending cortical and sensory inputs have many projections across the motoneuron pool (Lawrence et al. 1985; Ishizuka et al. 1979). These common inputs induce correlation between the motor unit spike trains that are active during a sustained contraction. However, only the low-frequency components of the neural drive are effectively reflected into the motor output of muscle (Mannard & Stein, 1973), since the contractile part of the muscle fiber acts as a strong low-pass filter. For this reason, the low-frequency components of the neural drive constitute the effective control signal to the muscle.

The aim of the Study II was to identify a common signal component that could be described in the best (linear) way the low-frequency oscillations of motor unit discharge rates and to investigate its relation with the force fluctuations generated by the muscle contractions. The analysis was performed on two muscles, abductor digiti minimi and tibialis anterior, using intramuscular fine-wire electrodes. Based on the results of the Study I, we applied also a new algorithm (Holobar & Zazula, 2004) to decompose surface EMG signals recorded by a high-density matrix of electrodes. Using the combination of the two techniques, we could identify the spike trains of large populations of motor units (~ 10), quite representative of the global activity of the muscle. The instantaneous discharge rate of each identified motor unit was smoothed using a 400-ms Hanning window and high-pass filtered with cut-off frequency 0.75 Hz (De Luca et al., 1982). The standard principal component technique (Jolliffe & Morgan, 1997) was applied to the set of smoothed discharge rates. The relative energy of the first principal component was used as an index to characterize the strength of the common oscillations in the activities of the motor neurons. The linear projection calculated from the first eigenvector was named first common component (FCC).

The FCC resulted to be representative of a large portion of the total variance of the discharge rates and showed high correlation and coherence with the force output in both muscles. Since the first common component was calculated using a relatively large set of motor units, but still very small compared with the actual number of motor units active, the results imply that the dimensionality of the controller is quite low and a large synaptic communality exists in the motoneuron pool. In agreement with the high correlation with the force signal, the coefficient of variation (CoV) for the FCC was strongly associated with the CoV for force in both muscles and all contraction forces. Conversely, the CoV for the ISI of the individual motor units was poorly correlated with the CoV for force. In addition, we demonstrated that the envelope of the surface EMG, due to amplitude cancellation, showed a weak correlation with both the FCC signal and force.

In conclusion, the Study II showed that the ensemble of low-frequency oscillatory components of motor unit discharge rates can be represented by a one-dimensional signal, obtained by linear transformation of the smoothed discharge rates, which explains most of the force oscillations.

III. Spatial variability of corticomuscular coherence.

The Study III focused on exploring the limitation of corticomuscular coherence analysis between EEG and surface EMG to assess descending oscillatory drives. The aim was to assess the variability of this measure over different locations on the muscle using multi-channel EMG and EEG recordings. Concurrent recordings from the leg area on the motor cortex and muscle activity over the tibialis anterior were performed during low level sustained isometric contractions (5, 7.5 and 10 % MVC). Surface EMG was recorded using a semidisposable adhesive grid of 64 electrodes (5-mm inter-electrode distance). Coherence function was computed between the EEG signals and all EMG channels.

The results showed that the frequency of the peak in corticomuscular coherence was confined in the range 15-30 Hz, as many previous studies at sub-maximal voluntary contractions have showed (Conway et al., 1995; Halliday et al., 1998), with a relatively low level of variability. However, the standard deviation of the peak magnitude of the coherence across the muscle was very high. Although a coherent oscillation is clearly present, due to the non-linearities between EEG and interference EMG signals, the technique showed to be not enough stable and reliable to quantify it.

The study thus demonstrated that the analysis of corticomuscular coherence for assessing descending drive to the motor neuron pool has limitations. These results leads to perform the analysis of the corticospinal inputs using a more direct measure than the surface EMG signals, the motor unit spike trains (Study IV).

IV. Linear transmission of cortical oscillations to the neural drive to muscles is mediated by common projections to populations of motor neurons in humans.

The EEG signal recorded from the primary motor cortex is coherent in the beta frequency band with the surface EMG signal detected over the contralateral muscles. The phenomenon presumably arises from the effective connections between the cortical and spinal motoneurons. However, the surface EMG is known to be only a crude estimation of the global activity of the motoneuron pool (Farina et al., 2004) and corticomuscular coherence has never been shown directly from the spike trains of motor units. In this study, we used EEG and intramuscular recordings from the abductor digiti minimi muscle in seven subjects to demonstrate the presence of coherence between the cortical input to motoneurons and the sum of the spike trains of a pool of identified motor units. Moreover, a simple theoretical derivation based on the work of Bayly (1968) and Nakao et al. (1997) was obtained to show analytically the experimental findings.

The results indicated that few motor units were sufficient to estimate a significant level of coherence between the EEG signals and the composite spike trains. This was confirmed by the theoretical derivation under the assumption of common inputs to the motoneuron pool. In particular, the transmission of the cortical input to motoneurons through the corticospinal tract is achieved because i) this input is largely common to all motoneurons, and ii) its frequency content requires only a small fraction of active motoneurons to be accurately sampled. In this way, the central nervous system can directly transmit oscillations to the control signals to muscles for practically the entire range of functionally relevant forces.

V. Effects of common spinal inputs on the estimation of the supraspinal contributions to motoneurons.

Common synaptic inputs are sampled by spinal motoneurons and this produces correlation between their output spike trains. Both cortical and spinal pathways induce common synaptic inputs between motoneurons in the spinal cord. Multiple common inputs, either excitatory or inhibitory, can influence each others and produce decorrelation effects (Maltfort et al., 1998). In Study V, we used realistic computational model to

investigate the cortical drive from the motor cortex on the activity of populations of motor units. The simulations were based on a model of populations of motoneurons (Cisi & Kohn, 2008) that received common (cortical and spinal) and independent inputs. A model of volume conductor and surface EMG generation was used to simulate the EMG signals (Farina et al., 2004). We investigated the influence of different common spinal inputs on the estimation of the corticomuscular coherence.

The results showed that the presence of a second common input (in addition to and independent from the cortical input) to the motoneuron pool, that could be a spinal input generated by afferent feedbacks for example, had a substantial influence on corticomuscular coherence estimates. Given a common cortical input to a motoneuron pool, another common signal can decorrelate the first from the output. The finding is very important, since it indicates that corticomuscular coherence is not a direct measure of changes in the strength of supraspinal modulation of the motoneuron output.

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CHAPTER VI

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Detecting the Unique Representation of Motor-Unit Action Potentials in the Surface Electromyogram

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Running title: Motor Units in the Surface EMG

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CHAPTER VII

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Fluctuations in isometric muscle force can be described by one linear projection of low-frequency components of motor unit discharge rates

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CHAPTER VIII

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Spatial variability of corticomuscular coherence

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CHAPTER IX

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Linear transmission of cortical oscillations to the neural drive to muscles is mediated by common projections to populations of motor neurons in humans

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CHAPTER X

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Decorrelation of cortical inputs and motoneuron output

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Running title: Transmission of cortical input to motoneurons

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CHAPTER XI

Conclusion

The execution of movements is the result of a complex chain of physiological events, coded by a combination of discrete events (action potentials), in subcortical and cortical structures, spinal cord circuitries, and muscle fibers. Motor neurons in the motor cortex are active during the execution of voluntary movements and their signals are sent through the pyramidal tracts to the spinal cord circuitries whose output layer is made of motor neurons. Motor neurons convert the synaptic inputs into electro-mechanical activation of the muscle.

In this thesis, we studied the functional contribution of descending drive and spinal pathways in isometric movements. Moreover, we focused on the techniques that are available for the estimation of the characteristics of those pathways and assessed strengths and limits of those. A better understanding of their behavior is important to improve rehabilitation treatments with impairment in some of these pathways.

In order to understand the characteristics of the control signal that drives the motor neuron pool, a reliable decoder of the neural information generated by the motor neuron pool is necessary. Since the use of the surface EMG in this context is limited by its feature of blurring the activity of multiple motor units, more investigations on the topic were needed. Study I (chapter VI) described a simulation study that was performed to assess if decomposition of multi-channel surface EMG can theoretically provide the means for separate the activity of a large number of motor units. This work was necessary to understand: 1) if the decomposition of surface EMG is a realistic approach for extracting superficial motor units; 2) which was the best spatial filter candidate and the number of electrodes needed for an accurate decomposition of the surface EMG. Study II (chapter VII) uses the knowledge gained from the previous study in order to overcome the main limitation that is present in most of the motor unit studies in humans, the relatively small number of motor neuron that can be analyzed concurrently during a sustained contraction. The combination of high-

density surface EMG and intramuscular recordings permitted to identify a relatively large number of motor units and investigate the dimensionality of the motor control in healthy subjects. Moreover, the results demonstrated that the low-frequency components of the motor neuron spike trains are effectively transmitted in the motor output and consist in the control signal to the motor neuron pool. The main control signal in human motor system is generated at the motor cortex level and it is related with the volitional adjustments of the movement. A common method to quantify the strength of the communication between the motor cortex and the motor neuron pool is the corticomuscular coherence. Study III (chapter VIII) focused on the limits of the technique when applied to high-density surface EMG. Since the spectral characteristics of the EMG signal across the muscle are highly variable (see chapter III), the results demonstrated that the variability of the magnitude of the corticomuscular coherence may strongly affect the estimation of the supraspinal contributions to the motor neuron pool. Since the previous study revealed that cortico-muscular coherence is a questionable technique for assessing supra-spinal control on motor-neuron pool, Study IV investigated how the cortical inputs are encoded directly in the output spike trains of populations of motor units. The experimental data and a theoretical derivation showed that sampling relatively few motor units is sufficient to accurately identify the corticospinal drive. However, the non-linearities introduced by the spiking nature of the motoneurons can still influence the measure and its variability and should be taken into consideration. Study V investigated, using a computational model, a second problem that limits a correct estimation of the corticospinal drive. The interaction between different correlated synaptic noises can influence and decorrelate the output spike trains of the motor neurons. This implies that, for example, an increase in the common afferent contributions (fatigue, muscle pain, etc...) may decrease the estimation of the corticomuscular coherence even if the effective cortical drive is unchanged.