J Physiol 601.1 (2023) pp 11–20

TOPICAL REVIEW

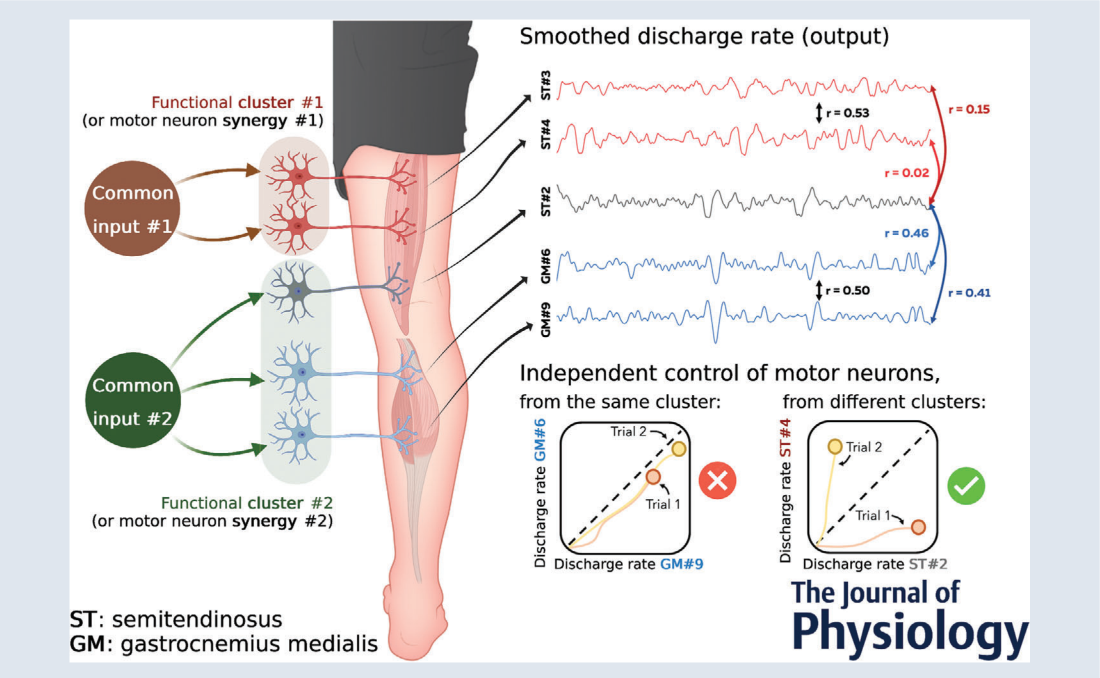
Common synaptic input, synergies and size principle: Control of spinal motor neurons for movement generation

François Hug[1,2], Simon Avrillon[3], Jaime Ibáñez[3,4,5] and Dario Farina[3]

[1] *Université Côte d'Azur, LAMHESS, Nice, France*
[2] *School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia*
[3] *Department of Bioengineering, Imperial College London, London, UK*
[4] *BSICoS, IIS Aragón, Universidad de Zaragoza, Zaragoza, Spain*
[5] *Department for Clinical and movement neurosciences, Institute of Neurology, University College London, London, UK*

Handling Editors: Laura Bennet & Mathew Piasecki

The peer review history is available in the Supporting information section of this article (https://doi.org/10.1113/JP283698#support-information-section).



François Hug received his PhD in human movement sciences from Aix-Marseille university, France (2003). He has been Full Professor at Nantes Université, France, where he led the MIP Lab until he moved to Université Côte d'azur, France, in 2021. He is a fellow of the Institut Universitaire de France and an honorary professor at the University of Queensland, Australia. His research focuses on the neural control of movement in health and disease. Within this area, he has (co)-authored more than 180 papers in peer-reviewed journals. **Dario Farina** has been Full Professor at Aalborg University and at the University Medical Centre Göttingen, where he founded and directed the Institute of Neurorehabilitation Systems, until he moved to Imperial College London as Chair in Neurorehabilitation Engineering. His research focuses on biomedical signal processing, neurorehabilitation technology and neural control of movement. Within these areas, he has (co)-authored more than 500 papers in peer-reviewed journals.

This article was first published as a preprint: François H, Simon A, Jaime I, Dario F. Common synaptic input, synergies, and size principle: Control of spinal motor neurons for movement generation. arXiv. https://doi.org/10.48550/arXiv.2208.02818

DOI: 10.1113/JP283698

Abstract Understanding how movement is controlled by the CNS remains a major challenge, with ongoing debate about basic features underlying this control. In current established views, the concepts of motor neuron recruitment order, common synaptic input to motor neurons and muscle synergies are usually addressed separately and therefore seen as independent features of motor control. In this review, we analyse the body of literature in a broader perspective and we identify a unified approach to explain apparently divergent observations at different scales of motor control. Specifically, we propose a new conceptual framework of the neural control of movement, which merges the concept of common input to motor neurons and modular control, together with the constraints imposed by recruitment order. This framework is based on the following assumptions: (1) motor neurons are grouped into functional groups (clusters) based on the common inputs they receive; (2) clusters may significantly differ from the classical definition of motor neuron pools, such that they may span across muscles and/or involve only a portion of a muscle; (3) clusters represent functional modules used by the CNS to reduce the dimensionality of the control; and (4) selective volitional control of single motor neurons within a cluster receiving common inputs cannot be achieved. Here, we discuss this framework and its underlying theoretical and experimental evidence.

(Received 18 September 2022; accepted after revision 7 November 2022; first published online 10 November 2022)

Corresponding authors F. Hug: Université Côte d'Azur, LAMHESS, 261 boulevard du Mercantour, 06200 Nice, France. Email: francois.hug@univ-cotedazur.fr; D. Farina: Imperial College London, White city campus 4th floor, London W12 0BZ, UK. Email: d.farina@imperial.ac.uk

Abstract figure legend In this review, we propose a new conceptual framework of the neural control of movement, which is based on the following assumptions: (1) motor neurons are grouped into functional clusters (or motor neuron synergies) based on the common inputs they receive; (2) clusters may significantly differ from the classical definition of motor neuron pools, such that they may span across muscles and/or involve only a portion of a muscle; (3) clusters represent functional modules used by the CNS to reduce the dimensionality of the control; and (4) selective volitional control of single motor neurons within a cluster receiving common inputs cannot be achieved. In this example, motor neurons innervating the semitendinosus (ST) do not necessarily receive common inputs (e.g. ST#2 *vs.* ST#3 and ST#4). Conversely, some motor neurons from the distant Gastrocnemius (GM) and ST muscles receive common inputs (e.g. ST#2 *vs.* GM#9 and GM#6).

Introduction

Understanding how movement is controlled by the CNS remains a major challenge, with ongoing debates about basic characteristics of its neural determinants. For example, the orderly recruitment of spinal motor neurons by size, as originally observed by Henneman (1957), is still challenged by studies reporting divergent recruitment orders across motor neurons from the same pool (Azevedo et al., 2020; Formento et al., 2021; Kishore et al., 2014; Marshall et al., 2022; Menelaou & McLean, 2012). Moreover, the possible strategies used by the CNS to reduce the computational burden of co-ordinating several thousand motor neurons across many muscles during natural movements have been proposed and debated for decades (Bernstein, 1947; Bizzi & Cheung, 2013; d'Avella & Bizzi, 2005; Latash, 2021; Tresch & Bizzi, 1999). In this review, we propose that a fundamental feature of movement control is the distribution of correlated synaptic inputs across groups of spinal motor neurones sharing functional roles. This contrasts with the classical vision of synaptic inputs being constrained by anatomical features, which is correlated inputs projected to an entire motor neuron pool. Understanding the structure of these correlated inputs may provide an important framework for a better understanding of how the CNS achieves two seemingly opposing goals: reducing the dimensionality of control and flexibly recruiting motor neurons to comply with various task constraints. Herein, we discuss this framework and the underlying theoretical and experimental evidence.

Inputs to motor neurons

Common input control. Each motor neuron transduces the synaptic input it receives into a series of action potentials that reach and excite an innervated group of muscle fibres, that is the muscle unit. A key role of the CNS in movement generation is to provide appropriate inputs to populations of motor neurons. As the final common pathway (Sherrington, 1906), the motor neuron receives inputs from descending, spinal interneuronal and sensory systems through thousands of synaptic connections. The net excitatory input that results from this synaptic bombardment can be considered an equivalent input current. A portion of this input is correlated across the motor neurons. We refer to this part of the input as common synaptic input and to the remaining portion as independent input (Fig. 1*A*).

Although both common and independent inputs to motor neurons theoretically contribute to the amount of force produced by the muscle, they have different effects on force modulation. Indeed, fine-tuning of the force level (i.e. modulation around a mean force) necessarily requires a concomitant and coherent activation of the muscle units (Farina et al., 2014; Negro et al., 2009). Therefore, volitional force modulation is mainly determined by common input, which results in common fluctuations in the discharges of motor neurons. Importantly, this does not necessarily imply that only common inputs are transmitted to motor neurons for force modulation but, instead, that a minimum amount of common input should be present in natural behaviour to voluntarily modulate muscle force.

Henneman's size principle imposes rigid control on motor neurons receiving common inputs. The size principle asserts that the physical dimensions of the soma and dendrites determine how readily a motor neuron is brought to spiking threshold. Smaller-sized motor neurons, which innervate weaker muscle units, possess a higher input resistance. Because of Ohm's law, changes in membrane potential will be greater in smaller motor neurons than in larger ones in response to equivalent synaptic currents. Consequently, across motor neurons receiving the same source(s) of synaptic input, the recruitment order of motor units should progress from those innervated by small neurons, producing weak forces, to those innervated by larger neurons, exerting greater forces (Henneman, 1957). Of note, a divergence, presumably small, may be observed if ionotropic or neuromodulatory inputs are not distributed uniformly across motor neurons, as discussed below. The combination of the size principle and common input is thought to be an effective way to reduce the computational load associated with controlling a large number of motor neurons (Henneman & Mendel, 1981). Importantly, such rigid control would be observed among the motor neurons receiving similar (i.e. common) input, regardless

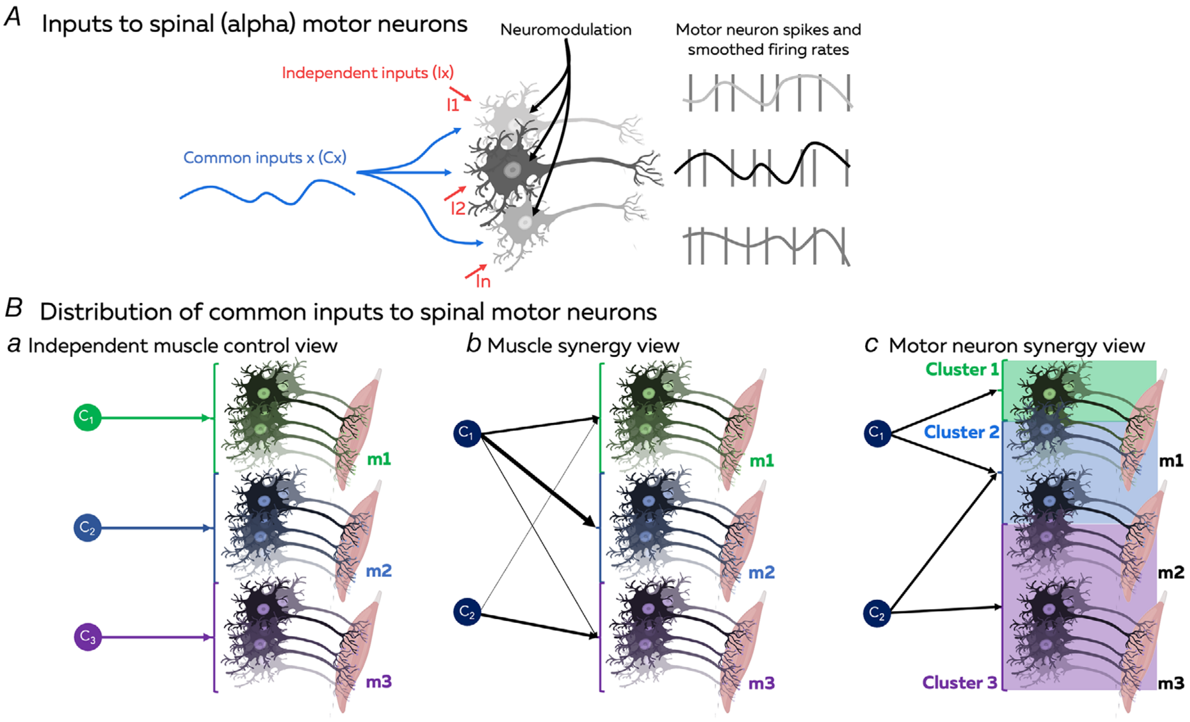


Figure 1. New conceptual framework for the distribution of common input to motor neurons
A, inputs received by spinal (alpha) motor neurons. In this example, each motor neuron receives a proportion of inputs shared with the other motor neurons (common inputs, Cx) from various possible sources and independent inputs (Ix). It is noteworthy that the intrinsic properties of the motor neurons may be independently modulated through neuromodulation. *B*, different scenarios for the distribution of common inputs to motor neurons. In the independent muscle control view, the entire pool of motor neurons (MNs) receives a single common input (C_i). In the muscle synergy view, the entire pool of motor neurons receives a set of common inputs with fixed weights, each common input being called a synergy. The framework that we propose [motor neuron synergy (or cluster)] considers that common inputs are not projected to the entire pool of motor neurons. Instead, they are projected to functional groups of motor neurons, which in turn project to the same or different muscles.

of the motor task. Conversely, motor neurons which receive different or independent inputs can theoreticallybe selectively recruited.

Conflicting evidence for common input control. Estimating common inputs to motor neurons during natural motor tasks is not straightforward. Indeed, it is not possible to measure the synaptic currents to motor neurons in humans; therefore, only indirect measures based on their output are possible. The correlation of motor unit discharge times [referred to as motor unit (short-term) synchronisation] (Heckman & Enoka, 2012; Sears & Stagg, 1976) has been widely used to infer the presence of common synaptic input to motor neurons. Nonetheless, the level of synchronisation between trains of action potentials of two motor neurons in their full bandwidth is not linearly proportional to the degree of common synaptic input to these motor neurons (de la Rocha et al., 2007). Consequently, the absence of synchronisation cannot be considered conclusive evidence for the absence of a common input. This is mainly explained by the fact that a motor neuron typically undersamples its synaptic input because of its relatively low discharge rate (<40 pulses s^{-1} for most muscles). This leads to a non-linear relationship between the input and the output signal, which is more pronounced at higher input frequencies. The non-linearity of the transmission of motor neuron inputs is further enhanced by the presence of additional non-linear transformation in the motor neuron behaviour related to the presence of persistent inward currents (Heckman & Enoka, 2012) and other ionic mechanisms such as slow inactivation of Kv1.2 channels (Bos et al., 2018). This problem can be mitigated by assessing the correlation between low-frequency oscillations of motor neuron discharge rates (Negro & Farina, 2012), a concept originally termed common drive (De Luca et al., 1982). The strength of the common drive can be estimated by applying a low-pass filter to the motor neuron discharge times before assessing their correlation (De Luca & Erim, 1994; Semmler et al., 1997).

Even though assessing whether motor neurons share a common input is challenging and influenced by factors that cannot be fully identified or compensated for, a combination of experimental results provides evidence of shared common inputs to motor neurons. Indeed, several studies have observed synchronisation or common drive to motor neurons innervating the same muscle (Schmied et al., 1994; Semmler & Nordstrom, 1995). In addition, synchronisation of motor neurons has been reported across synergist muscles; for example, between the vastus lateralis and medialis (Mellor & Hodges, 2005), extensor carpi radialis longus and extensor carpi ulnaris (De Luca & Erim, 2002), and medial gastrocnemius and soleus (Gibbs et al., 1995). The presence of such common input probably explains why, in a study where participants were provided with real-time feedback of the activity of pairs of motor neurons, they failed to volitionally control individual motor neurons (Bracklein et al., 2022).

Despite the aforementioned evidence for common input control, it is important to note that other studies have reported flexible control of motor neurons. Selective voluntary activation of single motor units has been suggested (Basmajian, 1963; Formento et al., 2021) and notable exceptions to the size principle have been reported (Azevedo et al., 2020; Basmajian, 1963; Desmedt & Godaux, 1981; Kishore et al., 2014; Marshall et al., 2022; Smith et al., 1980). For example, the recruitment order of motor neurons innervating the human interosseous muscle can change based on movement direction (Desmedt & Godaux, 1981). Violation of the size principle was also observed during rapid paw shaking behaviour in cats (Smith et al., 1980) or during rapid escape behaviours in zebrafish, where the most excitable motor neurons were not recruited (Menelaou & McLean, 2012). In addition, Marshall et al. (2022) observed behaviour-dependent patterns of motor neuron recruitment during isometric tasks performed under different mechanical constraints in macaques. These observations are often cited as evidence for inverted, rather than size-based, recruitment of motor neurons. Therefore, they are often used to support the capacity of the CNS to selectively target individual motor neurons.

In conclusion, there is conflicting evidence regarding purely common input control. As discussed below, we contend that changing the scale at which we observe and interpret common input to spinal motor neurons may reconcile previous divergent interpretations.

A new conceptual framework for the distribution of common input to spinal motor neurons. The concept of common input is often discussed at the level of the motor neuron pool, which is defined as the ensemble of motor neurons that innervate a muscle. Therefore, it is assumed (either explicitly or implicitly) that the full pool of motor neurons innervating a muscle receives similar (common) inputs (Fig. 1*B*, scenario a & b) (De Luca & Erim, 1994). This assumption is also made implicitly when studying muscle synergies (Fig. 1*B*, scenario b), defined as functional units that generate a motor output by imposing a specific activation pattern on a group of muscles (Cheung & Seki, 2021; d'Avella & Bizzi, 2005). Indeed, investigations on muscle synergies consider the muscle as the smallest functional unit of analysis (Giszter, 2015). Here, we introduce an alternative concept (Fig. 1*B*, scenario c), where common inputs do not necessarily project to all motor neurons in a pool but to groups of motor neurons that pertain to different pools. Specifically, this framework is based on the following assumptions: (1) motor neurons are grouped into functional groups (clusters) based on the common inputs they receive; (2) clusters may significantly differ from the classical definition of motor neuron pools, such that clusters of motor neurons may span across muscles and/or involve only a portion of a muscle; (3) clusters represent functional modules used by the CNS to reduce the dimensionality of the control; and (4) selective volitional control of single motor neurons within a cluster receiving common inputs cannot be achieved. The composition and number of clusters may change flexibly to accommodate a variety of tasks and learn new motor skills. Importantly, in addition to this organisation, motor neurons may receive distinct proprioceptive feedback signals, and their intrinsic properties may be independently modulated through neuromodulation (Heckman et al., 2008). This framework assumes that the CNS does not control muscles, but rather controls functional clusters of motor neurons, which could be considered as motor neuron synergies.

This proposed view merges the concept of common input to motor neurons with the synergistic control of movement, together with the constraints imposed on the recruitment order. It is a relatively small change of view with respect to, for example, the muscle synergy theory, although we consider that this change is important in explaining many divergent observations, as we will now discuss. Importantly, this framework can be tested experimentally. For example, two important interconnected predictions of the framework are (1) motor neurons from the same pool (i.e. innervating the same muscle) may receive different common inputs and at the same time (2) motor neurons from different pools (i.e. innervating different, including distant muscles) may receive common inputs.

Experimental evidence to support the control of functional groups of motor neurons. Substantial synchrony or common drive has been shown to exist for most pairs of motor neurons innervating a muscle (Bremner et al., 1991; Gibbs et al., 1995), leading to the long-held assumption that all motor neurons from a pool receive the same inputs (De Luca & Erim, 1994; De Luca et al., 1982). However, few studies have considered that these common inputs may not be distributed over the entire pool of motor neurons that innervate a muscle. These latter studies mainly focused on muscles in which individual motor units are spatially organised within discrete neuromuscular compartments (English et al., 1993). They observed that the recruitment of motor units from different regions may vary according to the mechanical constraints of the task (ter Haar Romeny et al., 1984). Thus, evidence exists, mainly on multi-tendoned muscles, that synchronisation between motor neurons is stronger within than between different muscle compartments (Keen & Fuglevand, 2004; McIsaac & Fuglevand, 2007; Reilly et al., 2004). Furthermore, results from a study by Madarshahian et al. (2021) support the notion that motor neurons from the flexor digitorum superficialis muscle form two groups that are controlled by two different (common) inputs. Recent studies have extended this observation to muscles that are not necessarily composed of neuromuscular compartments. The results of these studies suggest that, despite most pairs of motor neurons from the same muscle receiving common input, a significant proportion of them exhibit uncorrelated activity (Del Vecchio et al., 2022; Hug et al., 2022; Tanzarella et al., 2021). For example, Del Vecchio et al. (2022) identified two independent neural synergies that controlled motor neurons innervating the vastus lateralis and vastus medialis muscles during isometric constant-force contractions, but not all motor neurons innervating a muscle were controlled by the neural synergy mainly associated with that muscle. In other words, some motor neurons showed activity that correlated better with that of motor neurons innervating the other muscle than with the motor neurons innervating their ‘home’ muscle. Similarly, Tanzarella et al. (2021) factorised the low-frequency oscillations of the discharge rate of motor neurons from 14 hand muscles to identify neural synergies during isometric force-varying contractions. Although most of the motor neurons innervating the same muscle belonged to the same synergy, they again observed a proportion of motor neurons of the same muscle (between 6.4% and 16.7%, depending on the participant) that belonged to different synergies. Furthermore, Hug et al. (2022) decoded the spiking activities of dozens of spinal motor neurons innervating six lower-limb muscles during an isometric multi-joint task in humans. They identified subgroups of motor neurons that were partly decoupled from their innervated muscles. Specifically, subgroups of motor neurons from the same pool received different inputs, but shared common inputs with other subgroups of motor neurons innervating different, including distant, muscles (Fig. 2). Together, these observations are compatible with recent results obtained from both intramuscular and intracortical recordings made in macaque monkeys performing a variety of motor tasks, involving both sustained constant-force contractions and force-varying contractions. Specifically, in this latter study, the motor neuron behaviour was best explained by multiple drives rather than a unique common drive to the motor neuron pool (Marshall et al., 2022). Together, these results support the conceptual framework that motor neurons from the same pool do not necessarily receive the same synaptic input. Importantly, this evidence does not imply that some motor neurons from a certain pool are controlled through fully independent inputs with respect to all other neurons. Instead, it supports the claim that common inputs are projected onto functional groups of motor neurons rather than onto the entire pool.

Projections of inputs to functional groups of motor neurons may include projections to motor neurons from different pools. This is supported by several studies reporting common inputs distributed across muscles, including anatomically defined synergist (De Luca & Erim, 2002; Gibbs et al., 1995; Mellor & Hodges, 2005) and non-synergist hand muscles, such as between the extensor digitorum communis and flexor digitorum superficialis (Bremner et al., 1991) and between the flexor pollicis longus and flexor digitorum profundus (Hockensmith et al., 2005). Furthermore, Hug et al. (2022) observed correlated activity between motor neurons from adjacent muscles of different anatomical groups, for which cross-talk is not possible (e.g. between semitendinosus and gastrocnemius medialis) (Fig. 2). These results echo previous observations made by Gibbs et al. (1995), where the majority of participants exhibited synchronisation between the activity of motor neurons innervating the gastrocnemius and hamstring muscles. Although these studies could not determine the origin of the common synaptic input, their observations are compatible with the role of premotor interneurons (Levine et al., 2014; Ronzano et al., 2021) or corticospinal axons (Fetz & Cheney, 1980; Shinoda et al., 1981) in the projection of correlated inputs to motor neurons from different pools. For example, Ronzano et al. (2021) used intramuscular injection of viruses labelled with different fluorescent markers in mice and they observed that many of the individual premotor neurons in the spinal cord projected to motor neurons from different pools, including distant pools. In addition to these direct projections from common premotor neurons, correlated activity between motor neurons could also result from projections from separate premotor neurons having correlated activity resulting from receiving common inputs. This would provide additional flexibility for the control of the clusters of motoneurons or motor neuron synergies.

Together, these results imply that the CNS might control functional clusters of motor neurons rather than muscles. The proposed clustering of motor neurons based on

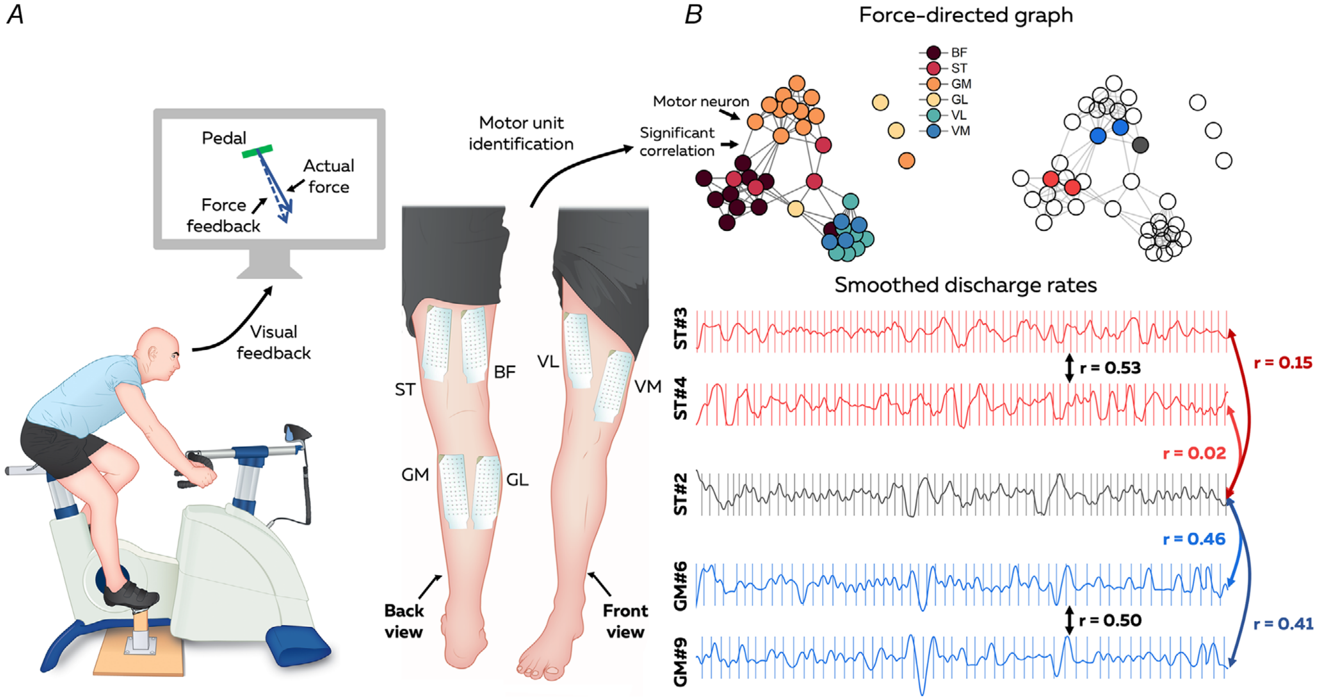


Figure 2. Experimental evidence to support the control of functional groups of motor neurons
In the study by Hug et al. (2022), participants performed an isometric multi-joint task, which consisted in producing force on an instrumented pedal (*A*). Adhesive grids of electrodes were placed over six lower limb muscles [gastrocnemius medialis (GM) and lateralis (GL), vastus lateralis (VL) and medialis (VM), biceps femoris (BF), semitendinosus (ST)] and the high-density EMG signals were decomposed into motor unit spike trains. They assessed the correlation between the smoothed discharge rates (*B*, with the discharge times depicted on the background) of each pair of motor neurons to determine whether they shared common input. Then, they used a data-driven method grounded on graph theory to extract networks of common inputs. In these graphs, each node represents a motor neuron and each edge represents a significant correlation between motor neurons. Data derived from their study support the framework proposed here (i.e. motor neurons innervating the same muscle do not necessarily receive common inputs) (ST#2 *vs*. ST#3 and ST#4) (*B*). Conversely, some motor neurons from different muscles, including distant muscles (ST#2 *vs*. GM#9 and GM#6), can receive common inputs. Of note, similar other examples can be identified from their data, available at https://figshare.com/s/dc7ce2758e4f3bbe6795.

common inputs has the main advantage of reducing the dimensionality of the control, at the same time as allowing flexibility in recruitment.

Implications for movement control

Modular control. The concept of synergistic control of movement has received considerable attention following its inception by Bernstein (1947). It is based on the assumption that grouping elements into stable groups reduces the number of variables to control and ultimately simplifies the production of movement. To date, the smallest unit of analysis within the synergistic model is the muscle, leading to the concept of muscle synergy (Cheung & Seki, 2021; d'Avella & Bizzi, 2005; Ting et al., 2015). Muscle synergies are identified by factorising the interference EMG signals from multiple muscles. This approach inherently constrains the dimensionality of the neural control to be less than or equal to the number of recorded muscles and relies on the underlying assumption that all motor neurons from a pool receive the same inputs, comprising the same common inputs with the same weight for the entire pool (Fig. 1*B*, scenario b). Indeed, the activation signal of the synergies is often represented as a projection to entire motor neuron pools (e.g. fig. 2 in Cheung & Seki, 2021; fig. 1 in Giszter, 2015). However, as proposed in our framework and supported by experimental data (Section 3), common inputs would not be projected to motor nuclei innervating muscles but, instead, across nuclei, partly irrespective of muscle innervation.

Grouping motor neurons into functional clusters might provide functional advantages. First, it reduces the initial large dimensionality of spinal motor neurons by grouping them into a smaller number of clusters. Control dimensionality is further reduced by the distribution of common inputs across clusters, which implies that the number of control signals for a given task may be smaller than the number of clusters. Notably, a reduction in dimensionality with respect to the number of motor neurons can also be achieved with common inputs distributed to motor neuron pools, as proposed by the classical views (Fig. 1*B*). However, the combination of functional clusters, as proposed by our framework, allows for a more flexible system relative to the classic muscle synergy control, where the pools of motor neurons rigidly receive the same inputs. By grouping motor neurons into functional clusters, the CNS can independently control motor neurons from the same muscle to comply flexibly with concurrent task constraints. For example, Hug et al. (2022) analysed an isometric multi-joint task that required the combined action of the gastrocnemii and hamstring muscles to extend the lower limb together with an action of the gastrocnemii muscles to orientate the output force at the foot. The observed organisation of motor neuron clusters reflected task demands; for example, it included both a cluster of motor neurons innervating the gastrocnemius and hamstring muscles and a cluster innervating the lateral and medial gastrocnemius muscles (Hug et al., 2022). Such an organisation may allow the CNS to independently control two motor actions, at the same time as reducing control dimensionality. In other words, these functional clusters may be recruited as functional units to control isolated knee flexion, isolated plantar flexion or combined knee flexion and plantar flexion. This functional advantage is not restricted to the control of the biarticular muscles. For example, the lateral and medial heads of the quadriceps share two main functions: producing knee extension torque and controlling the patellofemoral joint. The fact that the motor neurons from each of these muscles are not necessarily controlled by the same common input (Del Vecchio et al., 2022) may allow flexibility in independently controlling these important actions.

Further work is required to explore the robustness of this motor neuron grouping across different behaviours or mechanical constraints. Notably, this view of motor control modularity implies that conventional muscle synergy analysis is not appropriate for identifying the control dimensionality, whereas an analysis at the motor neuron level is necessary.

Recruitment order. Subsequent to the initial formulation of Henneman's size principle, notable exceptions have been reported, with a reversed order of recruitment (Azevedo et al., 2020; Desmedt & Godaux, 1981; Kishore et al., 2014; Marshall et al., 2022) or volitional independent control of motor units (Basmajian, 1963; Formento et al., 2021). Although these divergent observations are incompatible with the classical view of the size principle applied to the entire pool of motor neurons innervating a muscle, we contend that they can be explained by changing the scale at which the size principle is considered.

The relationship between the excitation threshold of a motor neuron and its size depends on underlying biophysical constraints (Caillet et al., 2022). Therefore, challenging Henneman's size principle is equivalent to challenging the presence of common input. The framework presented in Section 3 implies that the size principle applies to clusters of neurons that receive common inputs, rather than to motor neuron pools. Therefore, a reverse recruitment order can be observed between motor neurons from the same pool but from different clusters. It significantly differs from the interpretation that the activity of these motor neurons can be selectively modulated by the CNS (Basmajian, 1963; Formento et al., 2021). Specifically, a change in the order of recruitment between motor neurons belonging to different functional clusters may be achieved by changing the relative strength of the common inputs to these clusters. This was previously hinted at with perfect clarity by Bawa et al. (2014): '[…] when discussing recruitment order, the motoneuron pool should be operationally defined as the group of motoneurons that receive excitatory synaptic input to drive the functional movement, not the pool of motoneurons defined by anatomy. The validity of the size principle should then be evaluated within this operationally defined motoneuron pool to determine if recruitment proceeds from small to large'. Notably, further flexibility in recruitment within a functional cluster of motor neurons may be achieved through specific proprioceptive feedback signals and selective modulation of the intrinsic properties of motor neurons. However, in the absence of control of afferent feedback, the only way flexible control might be achieved is through modulation of inputs to different clusters.

Conclusions and future directions. We propose a conceptual framework of the neural control of movement, which merges the concept of common input to motor neurons and synergistic co-ordination of movement, together with the constraints imposed by recruitment order. A central feature of this framework is the distribution of common inputs to clusters of motor neurons, which partly overlap with the muscle innervation. Such a framework marks a transition from muscle synergy theory to motor neuron synergy theory. However, it is important to note that the structure of common inputs proposed in Fig. 1 may be more complex, such that clusters may partly overlap, allowing further flexibility in recruitment strategies, which leads to the important open question of the level of flexibility in motor neuron clusters. This question should be addressed through experiments performed on a vast repertoire of natural behaviours or virtual tasks decoupled from mechanical constraints. The results of such experiments may either confirm the proposed framework and may add new features to enrich it, or on the contrary, may disprove some parts of this view.

References

Azevedo, A. W., Dickinson, E. S., Gurung, P., Venkatasubramanian, L., Mann, R. S., & Tuthill, J. C. (2020). A size principle for recruitment of Drosophila leg motor neurons. *Elife*, **9**, e56754.

Basmajian, J. V. (1963). Control and training of individual motor units. *Science*, **141**(3579), 440–441.

Bawa, P. N., Jones, K. E., & Stein, R. B. (2014). Assessment of size ordered recruitment. *Frontiers in Human Neuroscience*, **8**, 532.

Bernstein, N. A. (1947). *On the construction of movements*. Medgiz.

Bizzi, E., & Cheung, V. C. (2013). The neural origin of muscle synergies. *Frontiers in Computational Neuroscience*, **7**, 51.

Bos, R., Harris-Warrick, R. M., Brocard, C., Demianenko, L. E., Manuel, M., Zytnicki, D., Korogod, S. M., & Brocard, F. (2018). Kv1.2 channels promote nonlinear spiking motoneurons for powering up locomotion. *Cell Reports*, **22**(12), 3315–3327.

Bracklein, M., Barsakcioglu, D. Y., Ibanez, J., Eden, J., Burdet, E., Mehring, C., & Farina, D. (2022). The control and training of single motor units in isometric tasks are constrained by a common input signal. *Elife*, **11**, e72871.

Bremner, F. D., Baker, J. R., & Stephens, J. A. (1991). Correlation between the discharges of motor units recorded from the same and from different finger muscles in man. *Journal of Physiology*, **432**(1), 355–380.

Caillet, A. H. D., Phillips, A. T. M., Farina, D., & Modenese, L. (2022). Mathematical relationships between spinal motoneuron properties. *Elife*, **11**, e76489.

Cheung, V. C. K., & Seki, K. (2021). Approaches to revealing the neural basis of muscle synergies: A review and a critique. *Journal of Neurophysiology*, **125**(5), 1580–1597.

d'Avella, A., & Bizzi, E. (2005). Shared and specific muscle synergies in natural motor behaviors. *PNAS*, **102**(8), 3076–3081.

de la Rocha, J., Doiron, B., Shea-Brown, E., Josić, K., & Reyes, A. (2007). Correlation between neural spike trains increases with firing rate *Nature*, **448**(7155), 802–806.

De Luca, C. J., & Erim, Z. (1994). Common drive of motor units in regulation of muscle force. *Trends in Neuroscience (Tins)*, **17**(7), 299–305.

De Luca, C. J., & Erim, Z. (2002). Common drive in motor units of a synergistic muscle pair. *Journal of Neurophysiology*, **87**(4), 2200–2204.

De Luca, C. J., LeFever, R. S., McCue, M. P., & Xenakis, A. P. (1982). Control scheme governing concurrently active human motor units during voluntary contractions. *Journal of Physiology*, **329**(1), 129–142.

Del Vecchio, A., Germer, C. M., Kinfe, T. M., Nuccio, S., Hug, F., Eskofier, B. M., Farina, D., & Enoka, R. (2022). Common synaptic inputs are not distributed homogeneously among the motor neurons that innervate synergistic muscles. *bioRxiv*, https://doi.org/10.1101/2022.01.23.477379.

Desmedt, H. E., & Godaux, E. (1981). Spinal motoneuron recruitment in man: rank deordering with direction but not with speed of voluntary movement. *Science*, **214**(4523), 933–936.

English, A. W., Wolf, S. L., & Segal, R. L. (1993). Compartmentalization of muscles and their motor nuclei: the partitioning hypothesis. *Physical Therapy*, **73**(12), 857–867.

Farina, D., Negro, F., & Dideriksen, J. L. (2014). The effective neural drive to muscles is the common synaptic input to motor neurons. *Journal of Physiology*, **592**(16), 3427–3441.

Fetz, E. E., & Cheney, P. D. (1980). Postspike facilitation of forelimb muscle activity by primate corticomotoneuronal cells. *Journal of Neurophysiology*, **44**(4), 751–772.

Formento, E., Botros, P., & Carmena, J. M. (2021). Skilled independent control of individual motor units via a non-invasive neuromuscular-machine interface. *Journal of Neural Engineering*, **18**(6), 066019.

Gibbs, J., Harrison, L. M., & Stephens, J. A. (1995). Organization of inputs to motoneurone pools in man. *Journal of Physiology*, **485**(1), 245–256.

Giszter, S. F. (2015). Motor primitives–new data and future questions. *Current Opinion in Neurobiology*, **33**, 156–165.

Heckman, C. J., & Enoka, R. M. (2012). Motor unit. *Comprehensive Physiology*, **2**, 2629–2682.

Heckman, C. J., Johnson, M., Mottram, C., & Schuster, J. (2008). Persistent inward currents in spinal motoneurons and their influence on human motoneuron firing patterns. *The Neuroscientist*, **14**(3), 264–275.

Henneman, E. (1957). Relation between size of neurons and their susceptibility to discharge. *Science*, **126**(3287), 1345–1347.

Henneman, E., & Mendel, L. (1981). Functional organization of motoneuron pool and its inputs. In *Handbook of Physiology - The nernous system*.

Hockensmith, G. B., Lowell, S. Y., & Fuglevand, A. J. (2005). Common input across motor nuclei mediating precision grip in humans. *Journal of Neuroscience*, **25**(18), 4560–4564.

Hug, F., Avrillon, S., Sarcher, A., Del Vecchio, A., & Farina, D. (2022). Correlation networks of spinal motor neurons that innervate lower limb muscles during a multi-joint isometric task. *Journal of Physiology*.

Keen, D. A., & Fuglevand, A. J. (2004). Common input to motor neurons innervating the same and different compartments of the human extensor digitorum muscle. *Journal of Neurophysiology*, **91**(1), 57–62.

Kishore, S., Bagnall, M. W., & McLean, D. L. (2014). Systematic shifts in the balance of excitation and inhibition coordinate the activity of axial motor pools at different speeds of locomotion. *Journal of Neuroscience*, **34**(42), 14046–14054.

Latash, M. L. (2021). Understanding and synergy: A single concept at different levels of analysis? *Frontiers in Systems Neuroscience*, **15**, 735406.

Levine, A. J., Hinckley, C. A., Hilde, K. L., Driscoll, S. P., Poon, T. H., Montgomery, J. M., & Pfaff, S. L. (2014). Identification of a cellular node for motor control pathways. *Nature Neuroscience*, **17**(4), 586–593.

Madarshahian, S., Letizi, J., & Latash, M. L. (2021). Synergic control of a single muscle: The example of flexor digitorum superficialis. *Journal of Physiology*, **599**(4), 1261–1279.

Marshall, N. J., Glaser, J. I., Trautmann, E. M., Amematsro, E. A., Perkins, S. M., Shadlen, M. N., Abbott, L. F., Cunningham, J. P., & Churchland, M. M. (2022). Flexible neural control of motor units. *Nature Neuroscience*, **25**(11), 1492–1504.

McIsaac, T. L., & Fuglevand, A. J. (2007). Motor-unit synchrony within and across compartments of the human flexor digitorum superficialis. *Journal of Neurophysiology*, **97**(1), 550–556.

Mellor, R., & Hodges, P. W. (2005). Motor unit synchronization is reduced in anterior knee pain. *The Journal of Pain*, **6**(8), 550–558.

Menelaou, E., & McLean, D. L. (2012). A gradient in endogenous rhythmicity and oscillatory drive matches recruitment order in an axial motor pool. *Journal of Neuroscience*, **32**(32), 10925–10939.

Negro, F., & Farina, D. (2012). Factors influencing the estimates of correlation between motor unit activities in humans. *PLoS One*, **7**(9), e44894.

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. *Journal of Physiology*, **587**(24), 5925–5938.

Reilly, K. T., Nordstrom, M. A., & Schieber, M. H. (2004). Short-term synchronization between motor units in different functional subdivisions of the human flexor digitorum profundus muscle. *Journal of Neurophysiology*, **92**(2), 734–742.

Ronzano, R., Lancelin, C., Bhumbra, G. S., Brownstone, R. M., & Beato, M. (2021). Proximal and distal spinal neurons innervating multiple synergist and antagonist motor pools. *Elife*, **10**, e70858.

Schmied, A., Vedel, J. P., & Pagni, S. (1994). Human spinal lateralization assessed from motoneurone synchronization: dependence on handedness and motor unit type. *Journal of Physiology*, **480**(2), 369–387.

Sears, T. A., & Stagg, D. (1976). Short-term synchronization of intercostal motoneurone activity. *Journal of Physiology*, **263**(3), 357–381.

Semmler, J. G., & Nordstrom, M. A. (1995). Influence of handedness on motor unit discharge properties and force tremor. *Experimental Brain Research*, **104**(1), 115–125.

Semmler, J. G., Nordstrom, M. A., & Wallace, C. J. (1997). Relationship between motor unit short-term synchronization and common drive in human first dorsal interosseous muscle. *Brain Research*, **767**(2), 314–320.

Sherrington, C. S. (1906). *The integrative action of the nervous system*. New Haven, CTYale University.

Shinoda, Y., Yokota, J., & Futami, T. (1981). Divergent projection of individual corticospinal axons to motoneurons of multiple muscles in the monkey. *Neuroscience Letters*, **23**(1), 7–12.

Smith, J. L., Betts, B., Edgerton, V. R., & Zernicke, R. F. (1980). Rapid ankle extension during paw shakes: selective recruitment of fast ankle extensors. *Journal of Neurophysiology*, **43**(3), 612–620.

Tanzarella, S., Muceli, S., Santello, M., & Farina, D. (2021). Synergistic organization of neural inputs from spinal motor neurons to extrinsic and intrinsic hand muscles. *Journal of Neuroscience*, **41**(32), 6878–6891.

ter Haar Romeny, B. M., van der Gon, J. J., & Gielen, C. C. (1984). Relation between location of a motor unit in the human biceps brachii and its critical firing levels for different tasks. *Experimental Neurology*, **85**(3), 631–650.

Ting, L. H., Chiel, H. J., Trumbower, R. D., Allen, J. L., McKay, J. L., Hackney, M. E., & Kesar, T. M. (2015). Neuromechanical principles underlying movement modularity and their implications for rehabilitation. *Neuron*, **86**(1), 38–54.

Tresch, M. C., & Bizzi, E. (1999). Responses to spinal microstimulation in the chronically spinalized rat and their relationship to spinal systems activated by low threshold cutaneous stimulation. *Experimental Brain Research*, **129**(3), 0401–0416.

Additional information

Competing interests

The authors declare that they have no competing interests.

Author contributions

F.H. and D.F. wrote the first draft of the article. All authors contributed to the definition of the framework proposed in this review, along with drafting the article and critically revising it for important intellectual content. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

François Hug was supported by a fellowship from the Institut Universitaire de France (IUF) and by the French government, through the UCAJEDI Investments in the Future project managed by the National Research Agency (ANR) with the reference number ANR-15-IDEX-01. Jaime Ibáñez was supported by a fellowship from 'la Caixa' Foundation (ID 100010434) and from the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie Grant Agreement No 847648 (fellowship code LCF/BQ/PI21/11830018). Dario Farina received support from the European Research Council Synergy Grant NaturalBionicS (contract #810346), the EPSRC Transformative Healthcare, NISNEM Technology (EP/T020970), and the BBSRC, 'Neural Commands for Fast Movements in the Primate Motor System' (NU-003743).

Acknowledgements

We thank Andrew J. Fuglevand (University of Arizona) for his insightful comments on the manuscript.

Keywords

common drive, electromyography, motor modules, motor primitives, motor unit

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History