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EDITORIAL

I am very pleased to have had the opportunity to organize this special issue on Brain and Movement for the Journal of Integrative Neuroscience (JIN). I genuinely thank the contributors, all leading neuroscientists, for the time and effort spent in writing highly readable and instructive papers.

The opening chapter by Daniel Zytnicki and Marin Manuel is on motoneurons, as it should be. The content is developed historically, but the emphasis is on mechanistic explanations of function and the review is very up to date. Next, John Van Opstal describes his model of how the superior colliculus controls saccadic eye movements. It is an example of science at its best, experimental work culminating in a mathematical theory. He also contributes to breaking down "barriers" by relating his work to studies of the motor cortical control of limb movements. The dark basements of the brain remain the basal ganglia (BG), as John Rothwell puts it in the third article of the series. Reading through his essay, however, one will feel satisfied by the progress made, the mechanistic explanation of at least one of the BG dysfunctions leading to akinesia/bradykinesia and the recent understanding of the BG in terms of actions leading to reward, or responding to salient inputs. In contrast, the cerebellum is not located in a basement of the brain. It sits conspicuously aside the brain and its basic circuit wiring has been understood since the late 1960s illustrating well the idea that knowing the circuit does not explain how it functions, or indeed what it does. Egidio D'Angello takes us on a tour of the cervelletto, the "little brain", in the fourth review article. He emphasizes the dynamic characteristics of the granular layer (input layer) as critical in cerebellar operations and reconciles the timing and learning hypothesis of cerebellar function, positing that the cerebellum learns to time.

Recovery of function following damage to the motor cortex has been known for a long time, the mechanisms of recovery, however, have only recently begun to be elucidated. The article by Warren Darling, Marc Pizzimenti and Robert Morecraft provides a historical perspective on studies of recovery following brain damage and describes their important neuroanatomical and neurobehavioural observations on the mechanisms of recovery. When the lateral motor cortex areas are damaged, medial cortical motor areas having extant corticospinal connections take over the direct cortical control of movement. The final article by Amir Karniel surveys the field of computational motor control, which has its roots in the cybernetics approaches of the 1950s and 1960s. Issues related to ideas of optimal movement

trajectory formation, optimal feedback control, internal models and their physiological basis are addressed.

A more complete coverage of the field would have included papers on cortical areas involved in motor control and neuroprosthetics. These omissions are unintentional. We, all who are involved, hope that the present review articles will be informative and motivating. Finally, we invite submissions of experimental work especially that accompanied by mathematical analyses.

Charles Capaday

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ALPHA, BETA AND GAMMA MOTONEURONS: FUNCTIONAL DIVERSITY IN THE MOTOR SYSTEM'S FINAL PATHWAY

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Since their discovery in the late 19th century our conception of motoneurons has steadily evolved. Motoneurons share the same general function: they drive the contraction of muscle fibers and are the final common pathway, i.e., the seat of convergence of all the central and peripheral pathways involved in motricity. However, motoneurons innervate different types of muscular targets. Ordinary muscle fibers are subdivided into three main subtypes according to their structural and mechanical properties. Intrafusal muscle fibers located within spindles can elicit either a dynamic, or a static, action on the spindle sensory endings. No less than seven categories of motoneurons have thereby been identified on the basis of their innervation pattern. This functional diversity has hinted at a similar diversity in the inputs each motoneuron receives, as well as in the electrical, or cellular, properties of the motoneurons that match the properties of their muscle targets. The notion of the diverse properties of motoneurons has been well established by the work of many prominent neuroscientists. But in today's scientific literature, it tends to fade and motoneurons are often thought of as a homogenous group, which develop from a given population of precursor cells, and which express a common set of molecules. We first present here the historical milestones that led to the recognition of the functional diversity of motoneurons. We then review how the intrinsic electrical properties of motoneurons are precisely tuned in each category of motoneurons in order to produce an output that is adapted to the contractile properties of their specific targets.

Keywords: Spinal cord; historical perspective; electrophysiological studies; physiological types of motor units; intrinsic properties of motoneurons; voltage-dependent currents.

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1. Introduction

Since the pioneering work of the great physiologist Sir Charles Scott Sherrington, it is widely recognized that a specific group of CNS neurons, called motoneurons, link the nervous system to the muscles. They are the final common pathway, i.e., the seat where all the peripheral and central neural pathways converge to elicit the motor output. A single motoneuron drives a subset of muscle fibers within a muscle, thereby defining the concept of motor unit [111]. Since Charles Sherrington's work we know the function of motoneurons: each of them transforms inputs arising from the numerous paths involved in motricity into an output that drives the contraction of the innervated muscle fibers. The Nobel Prize was awarded jointly to Sir Charles Scott Sherrington and Edgar Douglas Adrian, in 1932, "for their discoveries regarding the functions of neurons". The motoneurons are unique in the mammalian central nervous system, in the sense that they are the only neurons for which their function is so precisely known.

Moreover, the spinal motoneurons were the first central cells to be intracellularly recorded by one of Sherrington's pupils, John C. Eccles, who was awarded (alongside Hodgkin and Huxley) the Nobel Prize in 1963. Eccles designed elegant methods that allowed him and his numerous collaborators to decipher the many pathways that synapse onto motoneurons. This enterprise initiated by the Canberra group was pursued in Göteborg by Lundberg, Jankowska and many colleagues. A number of excellent reviews have already been written on this topic (see for instance [3, 84]). In the mean time Granit (who also was awarded the Nobel prize in 1967) initiated the study of the intrinsic properties of motoneurons [56]. His pupil, Kernell demonstrated that the discharge properties of motoneurons are well adapted to the mechanical properties of muscle fibers [92]. We had to wait the end of 1980s and the work of Hultborn and Hounsgaard in Copenhagen to discover that dendrites of motoneurons are not passive but endowed with active properties that play a critical role in the input−output transformation [69, 70].

Our conception of the motoneuron has considerably evolved since their discovery, when they were implicitly considered a uniform population. Nowadays, we know that they constitute indeed a very heterogeneous class of neurons. They differ by their function (that is, the muscle fibers they innervate), their intrinsic electrical properties, the pathways that control them, their molecular properties, and their susceptibility to degeneration. Provocatively, one may even argue that there is no such thing as a "canonical" motoneuron. The aim of this review is to explore the differences between classes of motoneurons. In the first part, we will review the historical milestones that led to the recognition of the enormous functional diversity of motoneurons. In the second part, we will review how the intrinsic electrical properties of motoneurons are precisely tuned in each category of motoneurons in order to produce an output that is adapted to the contractile properties of their specific targets. Our goal was not to make an exhaustive review of the literature, but instead to point out important physiological principles that we believe deserve attention in order to understand the motor system.

2. Motor Nuclei Comprise Many Functional Subclasses of Motoneurons: A Brief Historical Summary

2.1. *Two distinct populations of motoneurons: Alpha and gamma motoneurons*

Since the discovery of muscle spindles by Kölliker [96] in frog and by Kühne [99] in mammals, we know that muscle spindles contain a bundle of thin muscle fibers that look different from the ordinary muscle fibers. A first milestone, remarkably summarized in Matthews's monograph [120], was the recognition that, in a muscle nerve, only the largest motor axons innervate the ordinary muscle fibers whereas the smallest specifically innervate the intrafusal muscle fibers. Already, Eccles and Sherrington [45] clearly demonstrated, after degeneration of the afferent fibers, a bimodal distribution of the motor axon diameters. However, they believed that the smallest fibers branched less than the largest ones and that they innervated fewer ordinary muscle fibers. Surprisingly, they overlooked at that time the possibility that the two different sizes of motor axons might have different functions despite the fact that Langley [101] has proposed few years earlier that the smallest axons might specifically target the spindles.

The two populations were called "alpha" and "gamma" motor axons on the basis of electrophysiological experiments demonstrating that small motor axons with high electrical threshold conduct the action potentials more slowly than large motor axon with low electrical threshold. Indeed, Erlanger, Bishop and Gasser [52] showed, in frogs, that the large motor fibers contribute to the first peak of the compound action potential recorded on the ventral roots upon stimulation of the sciatic nerve. They called this peak the "alpha peak". Later on, Leksell [107], in Granit's laboratory, demonstrated in cat experiments that another wave, which he named the "efferent gamma wave", appeared when the stimulation was increased about four times the threshold for the most excitable fibers in the alpha peak. Leksell found that the motor axons in the gamma wave conduct the action potentials at much slower velocities than the fastest axons in the alpha peak. The fast and slow conducting fibers in the alpha and gamma peaks were then routinely called alpha and gamma motor axons in the Granit laboratory. By extension, the corresponding cell bodies in the ventral horn were called alpha and gamma motoneurons. This nomenclature has been rapidly adopted by the community of motor system physiologists.

2.2. *Alpha and gamma motoneurons have different functions*

Elegant electrophysiological works provided the definitive demonstration of the fusimotor function of small axons and the ordinary function of the large ones. Matthews [117] was the first to demonstrate an excitation of spindle afferents when increasing the stimulation of the nerve above that required to cause the maximal contraction of the muscle. By selectively blocking the large axons with a mechanical pressure applied on the nerve, Leksell [107] was able to demonstrate that the

stimulation of gamma fibers did not elicit any force at the tendon and that they, therefore, do not have the same function as the largest motor axons. This conclusion was later confirmed by Kuffler, Hunt and Quilliam [98] who, using their novel elegant technique of isolation of a single functional motor axon in the ventral root (and single functional afferent fiber in the dorsal root), demonstrated that the stimulation of a single gamma motor axon did not produce any force. Instead, stimulation of a gamma axon increased the discharge from single spindle afferent endings. Each spindle afferent was influenced by a number of gamma motoneurons with axonal conduction velocities ranging from 15 to 55 m/s [76, 97].

2.3. *Two subtypes of gamma motoneurons*

It was recognized early that spindles bear two types of sensory endings: the primary ending, innervated by the Ia afferent fiber, and secondary endings innervated by group II fibers [75]. Cooper [37] was the first to show that primaries and secondaries do not exhibit the same sensitivity to muscle stretches. She found that only primary endings are sensitive to dynamic stimuli, i.e., their rate of discharge increases with the stretch velocity, whereas the secondary are relatively insensitive, i.e., their firing rate does not depend on the velocity. These results were largely confirmed by Matthews *et al.* on de-efferented spindles (ventral roots cut) in which any fusimotor action was eliminated [118]. An elegant demonstration of differences between primary and secondary endings was further given by Bessou and Laporte [13] when they recorded from one afferent of each type belonging to the same spindle situated in the tenuissimus muscle of the cat. A consensus was soon reached; primary endings exhibit a strong dynamic sensitivity, whereas secondary endings have a better ability to encode muscle length, i.e., a higher static sensitivity.

During that time, the effects of stimulating single gamma motor axons, isolated in ventral root filaments, on the response of primary and secondary endings to stretching were also found to be of two types. In Bessou and Laporte's work, a gamma axon was found to increase the dynamical response during the stretch of the primary ending but had virtually no effect on a secondary ending of the same spindle [13]. This was a fusimotor axon with a "dynamic" action. Reciprocally, another gamma axon had no effect on the dynamic sensitivity of the primary ending but increased the response of the secondary endings. This axon had a "static" action only. At the same time, Matthews and his collaborators extensively investigated the actions of gamma axons on primary endings during servo-controlled stretches [20]. In their experiments, the dynamic sensitivity of primary endings was quantified using a "dynamic index". The gamma motor axons were classified in dynamic or static depending on their effects on responsiveness of primary endings during the ramp stretch. The dynamic gamma axons increased the dynamic index of primary endings whereas static gamma axons caused a decrease in the dynamic response even though they increased the overall excitability of the ending. A further argument in favor of two gamma axon types was given by experiments in which the action of a

single gamma axon was investigated in several spindles. Each gamma axon has the same fusimotor effect, either dynamic or static, in every spindle it innervates [14, 19]. This provides the best evidence that the classification between dynamic and static gamma axons genuinely reflects functional properties.

It was further known that the spindles contain two main types of intrafusal fibers: the nuclear bag fibers with relatively large diameter and long length, and the nuclear chain fibers with small diameters and relatively short length [4]. This led Matthews [119] to hypothesize that the differential effects of the dynamic and the static gamma axons could be explained if they respectively innervated nuclear bag fibers and nuclear chain fibers with different viscoelastic properties. This view proved, however, to be incorrect, but not far off the mark. Indeed, degeneration experiments showed that gamma axons can innervate both nuclear bag fibers and nuclear chain fibers [6]. Moreover, remarkable experiments carried out by Bessou and Pagès [15] and by Boyd, Gladden, McWilliam and Ward [16], in which electrophysiological recordings (action of a single gamma motor axon on a primary ending) were coupled to kinematic analysis of the contraction of intrafusal fibers, demonstrated that: (1) the dynamic gamma axons innervate a single nuclear bag fiber (that was shown to contract slowly); and (2) the static gamma axons innervate the other nuclear bag fiber (that displays a fast contraction) and/or the nuclear chain fibers. Experiments using the glycogen depletion method later on confirmed the selective innervation of dynamic and static gamma axons [18].

To summarize, in addition to the classical alpha motoneurons, there is a specific class of motoneurons, the gamma motoneurons, which innervate the mammalian muscle spindles (Fig. 1). These motoneurons allow a control of the spindle sensitivity that is independent of the control of the motor units. Among the gamma motoneurons, some (the gamma dynamic motoneurons) innervate only the bag1 fiber and they act by enhancing the dynamic sensitivity of the primary ending. The others (gamma static motoneurons) innervate the bag2 fiber and the chain fibers and they mainly act by enhancing the overall stretch sensitivity of primary and secondary endings.

2.4. *Three main subtypes of alpha motoneurons*

The recognition that alpha motoneurons innervate different physiological types of muscle fibers (Fig. 1) arose in parallel with the distinction of the subtypes of gamma motoneurons. Indeed, we know since Ranvier's work [137] that the contraction is slower in red muscles than in pale ones. Histological studies has revealed that most mammalian skeletal muscles are made of a mosaic of muscle fibers with different histological characteristics (see [33] for a review). The technique of isolation of a single functional motor axon in the ventral root allowed investigating the force (isometric force recorded at the tendon) and the physiological properties of single motor units. This enterprise was initiated by Laporte's and Henneman's groups. It was shown that the fastest conducting axons supply large motor units (large force) that contract with a high speed whereas slow conducting axons supply small motor

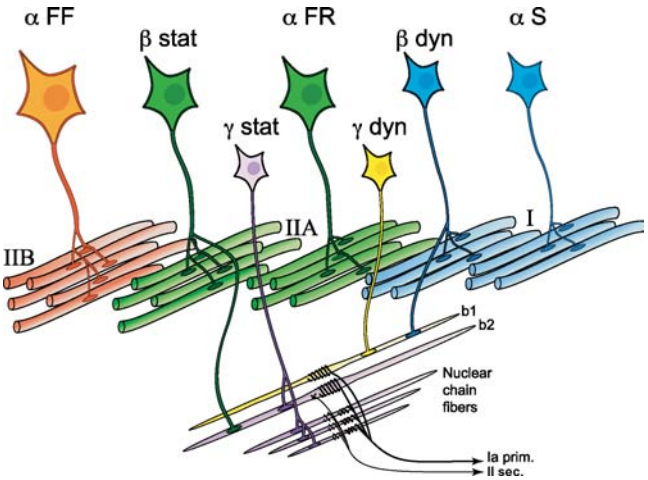


Fig. 1. Schematic representation of the different types of motoneurons. The figure represents seven motoneurons innervating either extrafusal or intrafusal muscle fibers. FF-type alpha motoneurons are the biggest motoneurons (in term of soma size and axon diameter), and innervate a large number of type IIB extrafusal muscle fibers. FR alpha motoneurons are slightly smaller and innervate type IIA extrafusal muscle fibers. S-type alpha motoneurons are the smallest of the alpha motoneurons, they innervate fewer type I muscle fibers. Beta motoneurons are skeleto-fusimotor: they innervate both extrafusal and intrafusal muscle fibers. Beta static motoneurons innervate either type IIA or IIB extrafusal fibers and the intrafusal bag2 fiber. Beta dynamic motoneurons innervate type I extrafusal muscle fibers and the intrafusal bag1 fiber. Gamma motoneurons innervate exclusively intrafusal muscle fibers and are the smallest of the motoneurons. Gamma static motoneurons innervate the intrafusal bag2 fiber and/or the nuclear chain fibers. Gamma dynamic motoneurons innervate the intrafusal bag1 fiber. Note that in a muscle, the various types of extrafusal muscle fibers are mingled together and organized in a mosaic, while the intrafusal muscle fibers are much smaller than the extrafusal fibers and are ensheathed in the spindle capsule. Primary and secondary endings of the spindle encode parameters of the muscle stretches that are sent to the central nervous system via afferent fibers Ia and II.

units that contract slowly [11, 150]. Each muscle was shown to contain motor units with a wide range of physiological properties and it was assumed that these properties must be related in some way to the molecular properties of their muscle fibers.

Progress of histochemistry in the 1960s revealed the ATPase activity (mitochondrial and myofibrillar), the content in mitochondrial oxidative enzymes (succinic dehydrogenase, NADH dehydrogenase) and the glycolytic activity of muscle fibers. Many classification systems of muscle fibers have then been proposed (for a review see [33]). Most of them distinguished three histochemical profiles of muscle fibers. In particular, Brooke and Kaiser [17] classified the muscle fibers into types I, IIA and IIB. This classification was based on the ATPase reactivity pattern of muscle fibers. Later on, it was shown that isoforms of myosin heavy chains are differentially expressed in the different types of muscle fibers, and nowadays classification of muscle fibers relies instead on immunohistochemistry of myosin heavy chains (for a review see [140]).

Edström and Kugelberg [47] were the first to use a method based on the depletion of glycogen in order to map the territory occupied by muscle fibers of a single motor

unit. Following a prolonged repetitive stimulation of a single motor axon, the glycogen is depleted in the innervated muscle fibers that can be revealed in cross muscle sections using the periodic acid-Schiff reaction. Succinic dehydrogenase and phosphorylase activities of the depleted muscle fibers were assessed in serial sections. This allowed them to investigate the "histochemical profile" of the muscle fibers and to correlate this profile with the physiological characteristics of the motor unit. They found a correlation between resistance to fatigue and activity of oxidative enzymes, but they did not find any relation between the twitch contraction time and histochemical profile. Moreover, the fibers of a given motor unit were not spatially grouped but scattered within the muscle.

A decisive progress was made by Burke *et al.* [26, 27] who combined intracellular stimulation of motoneurons innervating the gastrocnemius muscles with the glycogen depletion method. They found that two physiological parameters were best suited to separate the motor unit population into three physiological types. The first parameter was the presence or the absence of a sag on an unfused tetanus produced by a stimulus train in which the period was about 1.25 times the contraction time of the motor unit. The sag was present on the fast contracting motor units and absent on the slow contracting ones. The second parameter was the fatigue index. Burke *et al.* developed a stimulation paradigm (intermittent tetanization, i.e., short tetanus repeated every second during two minutes) that did not fatigue the neuromuscular transmission but induced some fatigue in the muscle fibers themselves. The fatigue index (ratio of the tetanus force at 2 minutes to the initial tetanus force) allowed them to distinguish fatigable motor units (fatigue index < 0.25) from resistant motor units (fatigue index > 0.75). It appeared that all motor units without sag were fatigue resistant, and they were thereafter called slow contracting motor units (S type). Most of the motor units that displayed a sag were either fatigable (fast contracting fatigable motor units, FF type) or fatigue resistant (FR type). A few fast contracting motor units had an intermediate fatigability (FI type). Thanks to the glycogen depletion method, Burke *et al.* [26, 27] further demonstrated that all the muscle fibers of a given motor unit exhibited the same histochemical profile. Furthermore, they found a correlation between the physiological type and the histochemical profile: type S motor units have type I muscle fibers, type FR motor units have type IIA muscle fibers, and type FF motor units have type IIB muscle fibers. The glycogen depletion technique also allowed counting the numbers of fibers in a single motor unit (i.e., the "innervation ratio"). The largest number was found in the FF motor units and the smallest in the S ones (intermediate number in the FR motor units) [28]. This fitted with the fact that FF motor units had the fastest axonal conduction velocity (presumably because the large number of axonal intramuscular branches necessitate a large diameter axon) and developed the highest force whereas S motor units had the slowest axonal conduction velocity and developed the smallest force. Since this pioneering work, the three physiological types of motor units have been demonstrated to be present in many skeletal muscles, not only in cats, but also in many mammal species including humans [23].

The experiments done by Burke *et al.* were indeed very powerful. Since the motoneurons were stimulated with an intracellular microelectrode, the authors could also record the basic intrinsic properties of motoneurons. They were then able to correlate these properties with the physiological type. Their work contributed to show (along with many works from different groups including Henneman's group) that the electrical properties of the motoneurons are in keeping with the supposed function of the motor unit (S and FR motor units likely involved in postural activity, FF motor units likely involved in transient and powerful movements; see below part II, and also [23] for a review). The demonstration by Burke *et al.* that motor units can be classified within three physiological types that correlate well not only with the three histochemical profiles of muscle fibers but also with the electrical properties of the motoneurons proved to be conceptually most important.

2.5. *The beta motoneurons: A third distinct category of motoneurons*

The specific innervation of intrafusal muscle fibers by gamma motoneurons seems to be the result of the evolution since it appears only in mammals. In lower vertebrates, such as amphibian and reptiles, the intrafusal innervation arises from branches of the same axons as those that innervate the ordinary (extrafusal) muscle fibers [144]. These axons have been called skeleto-fusimotor axons, or beta axons. However, it should be noted that the name beta does not refer to the conduction velocities of these axons and was chosen only to differentiate them from the alpha and gamma axons.

It was long discussed whether or not mammalian spindles are also innervated by skeleto-fusimotor axons in addition to their specific gamma innervation. Definitive answer to this question was provided by elegant experiments carried out by Laporte's group. To be undoubtedly identified as skeleto-fusimotor, an axon must produce both an extrafusal contraction and an excitation on spindle ending. However, the difficulty of the experiments was to differentiate the *direct* activation of the spindle ending that is elicited by the contraction of intrafusal fibers themselves from the *indirect* activation that could be caused by a passive stretching of the ending due to the contraction of adjacent extrafusal fibers. The demonstration of the direct character of the spindle activation is required to identify with certainty the axon as skeleto-fusimotor. On a very small cat muscle (the first deep lumbrical muscle) that contains less than 10 motor units, Bessou *et al.* [10, 12] stimulated, in ventral root filaments, single motor axons innervating this muscle while they recorded in dorsal root filaments afferent fibers innervating primary spindle endings of the same muscle. They found that some slowly conducting axons (that innervate slow contracting motor units) elicit a direct activation of spindle primary endings. Their demonstration relies on two observations: (1) The firing frequency of the spindle ending still increased when the stimulation frequency of the axon was increased above the frequency that elicits the maximal contraction of the motor unit (tetanic

fusion frequency). (2) The discharge of the primary ending persists after a light curarization sufficient to block completely the neuromuscular transmission to extrafusal muscle fibers but not the neuromuscular transmission to intrafusal muscle fibers. Both observations indicate that the spindle activation was not correlated with the extrafusal contraction and point out to a skeleto-fusimotor innervation. Interestingly, Bessou *et al.* [12] also showed that the presence of the beta innervation does not preclude a concomitant gamma innervation. The same spindle might be innervated both by one beta axon and by gamma axons with dynamic and static actions. Neuroanatomical evidence of the beta innervation was soon provided. Adal and Barker [1] were able to trace under microscope the innervation of the first deep lumbrical muscle. They found that some axons innervate both extra- and intrafusal fibers confirming the presence of beta axons. In the steps of Laporte's group, physiological arguments in favor of beta innervation was also provided for rat tail muscles [93] and cat tibialis posterior muscle [19].

2.6. *Two subtypes of beta motoneurons: Slow contracting motor units have a dynamic action on spindle endings; fast contracting motor units have a static action on spindle endings*

In their pioneering experiments, Bessou *et al.* [10, 12] have also investigated the action of the beta axons on the responsiveness of the primary ending during a muscle stretching. They found that these axons increased the dynamic sensitivity of the ending. Barker's group and Laporte's group then joined their efforts to use the glycogen-depletion method in order to study the intra- and extrafusal fiber types involved in the beta-innervation pattern. The dynamic beta axons were found to innervate the bag1 intrafusal muscle fiber, i.e., the effector of dynamic action, and extrafusal muscle fibers of the I type, i.e., the slow contracting motor units (see Fig. 2 and [5]).

Interestingly, in rabbit lumbrical muscles, Emonet-Denand *et al.* [49] using the same methods as in Bessou *et al.* [10, 12], found that despite the fact that most beta axons have a dynamic action on spindle primary endings, a fraction of them instead elicit static actions. However, a systematic investigation in various hindlimb muscles of the cat carried out by the same experimentalists [50] have revealed only exceptionally the presence of beta axons with static action. Almost all of the beta axons were found to elicit a dynamic action in cat muscles. Moreover, most dynamic beta axons have relatively slow conduction velocities (between 40 and 85 m/s, [50]). It was then speculated that the discrepancy between rabbit and cat experiments might be due to the fact that, for some reason, the intrafusal neuromuscular junctions, and particularly those of the chain fibers, are more sensitive to curare in the cat spindles than in the rabbit spindles. In cats, the neuromuscular junctions of the chain fibers are blocked as easily as the neuromuscular junctions of the extrafusal fibers precluding the use of the differential curarization test to identify static beta axons.

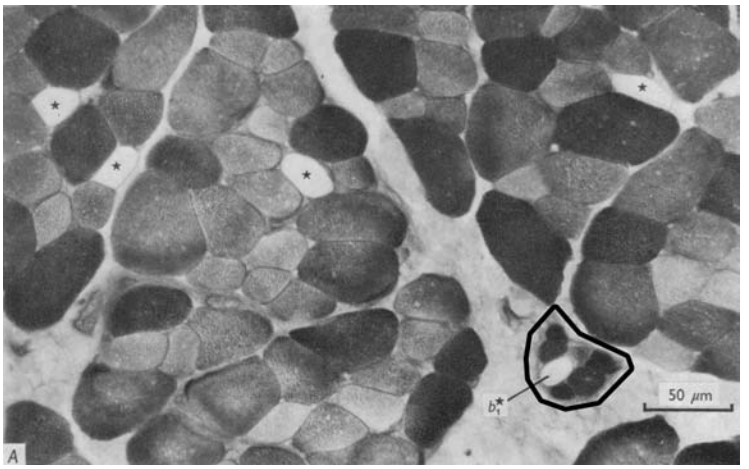


Fig. 2. Glycogen-depletion method revealing extrafusal and intrafusal muscle fibers innervated by a beta axon. An axon, with a faster conduction velocity (77 m/s) than gamma axons, was found to both increase the dynamic response to a muscle stretch in three spindles and to activate ordinary fibers in the cat peroneus brevis muscle. Glycogen depletion was obtained by the repetitive stimulation of the axon during which the blood flow was reduced by occluding the artery that supplied the muscle. After freezing, the muscle was cut in 10-mm thick sections. The present plate shows a section stained for glycogen using the periodic acid-Schiff (PAS) method. In the spindle visible on this plate (circled), the b1 fiber was depleted indicating that it was innervated by the axon (the b1 fiber of two other spindles were also depleted). In addition, extrafusal fibers (four on this plate, pointed out by asterisks) were depleted from their glycogen. Histochemistry on serial sections of myofibrillar ATPase activity and succinate dehydrogenase activity showed that these extrafusal fibers were of type I. Adapted from Barker *et al.* [5], with permission.

However, histophysiological studies using the glycogen-depletion method actually suggested the presence of static beta innervation in cat muscles [62, 81]. In these studies, the prolonged stimulation of groups of motor axons with fast conduction velocities (above 85 m/s) was found to induce a glycogen depletion essentially in nuclear chain fibers, i.e., the effectors of static actions, and more specifically in the longest of the chain fibers [62, 81]. In three experiments, in which a single fast-conducting motor axon was investigated, the depleted extrafusal muscle fibers were of the group IIA type, i.e., fast contracting and fatigue resistant motor unit [82].

Jami *et al.* [83] then designed new physiological tests that revealed the presence of static beta axons in the peroneus tertius, a small muscle of the cat. Beta static axons were identified using a combination of several protocols: (1) A differential fatigue of the neuromuscular junctions of extrafusal and intrafusal muscle fibers was elicited by prolonged periods of stimulation at 100−250 Hz. The fact that the activation of the spindle primary ending outlasts the complete block of the extrafusal contraction was taken as a sign of intrafusal action of the axon. (2) The excitation of spindle excitation should increase with stimulation frequencies above that eliciting maximal extrafusal contraction. (3) The discharge of the primary ending should still be modulated by these high stimulation frequencies. This indicated that the beta axon innervates intrafusal chain fibers that are known to exhibit tetanic fusion frequency

much higher than the extrafusal fibers. (4) Finally, the stimulation of the beta axon should exert a static action on the response of the spindle to ramp stretches.

Jami *et al.* [83] tested a large number of motor axons in the alpha range of conduction velocities. Among them, 21% proved to be static beta axons and 10% were dynamic beta axons (a total of 31% of the axons were thus beta axons). This figure was likely to be conservative since it was not possible in each experiment to test the action of every motor axon in all the spindles. Convergence on the same spindle of two (generally one static and one dynamic) or even three beta axons was frequently observed. Furthermore, the physiological type of the extrafusal muscle fibers was assessed using the same protocol as Burke *et al.* [26] (see above). Remarkably, all but one beta axons with static intrafusal action innervated FR or FF motor units whereas all but one beta axons with dynamic intrafusal action innervated S-type motor units (Fig. 1). The relative incidence of static versus dynamic beta axons depends on the proportion in FR/FF versus S motor units. The peroneus brevis (in which S motor units predominate) has more dynamic beta axons and less static beta axons than the peroneus tertius, in which FR/FF motor units predominate [51]. Dynamic beta effects occur when slow-contracting motor units are recruited. Since the dynamic sensitivity of primary endings is increased, one might speculate that dynamic beta motoneurons help to restore the balance and to maintain the posture. Static beta effects are related to the recruitment of fast-contracting motor units. One might speculate that they prevent the discharge rate of spindle endings from slowing or even from pausing during rapid muscle shortening. The fact that in mammalian muscles about one third of motor units are indeed "beta units" and that about three out of four spindles are beta innervated [51] indicate that beta motoneurons play a significant part in the regulation of spindle activity and consequently in the control of posture and movement.

To summarize, it is now clear that the mammalian spindles are innervated by both gamma and beta motoneurons. Similarly to gamma motoneurons, beta motoneurons exert both dynamic and static actions in the spindle endings. However, the intrafusal and extrafusal innervations of beta motoneurons is very precisely organized (Fig. 1). Dynamic beta motoneurons innervate the intrafusal bag1 fiber and the extrafusal slow contracting fibers (S-type motor unit). Static beta motoneurons innervate the longest of the intrafusal chain fibers and the extrafusal fast-contracting fibers (FR or FF motor units).

3. Differences in Electrical Properties Create Subtypes of Motoneurons That are Functionally Adapted to Their Targets

As we have discussed so far, even though motoneurons share a common function, to elicit muscle fiber contraction, there are many different muscle fibers: intrafusal fibers (among them the bag1 fiber whose mechanical properties are very different from those of bag2 and chain fibers) and extrafusal fibers which can be slow contracting, fast contracting, fatigable or fatigue resistant (each extrafusal fiber is

innervated by a single motoneuron). The contractile properties of the muscle fibers also depend on the function of the muscle. It is clear that flexing one's biceps is a vastly different task than protruding one's tongue or producing an eye saccade. Among different species, it might also be self evident to the reader that the properties of the muscles of a tiny animal like the mouse need to be different than those of a larger animal like an elephant, or even a man. This extraordinary functional diversity has hinted, especially since the works of Burke, at a diversity in the electrical, or cellular, properties of the motoneurons that innervate different types of muscle fibers. Even though the notion of the diverse properties of motoneurons has been extensively studied, it tends to fade away in today's scientific literature, where all the motoneurons become a single cell population, which develop from a given population of precursor cells, and which express a common set of molecules. The aim of this section is therefore to provide an overview of the differences that can nevertheless exist between cells that are remarkably similar to each other, but still need to exhibit different electrical responses to produce a force adapted to their function. The description of the various channels expressed by motoneurons was the subject of several excellent recent reviews [21, 65, 132], and we will therefore only focus on the properties that differ between motoneurons.

Unfortunately, very little is known about the properties of gamma motoneurons, mostly because of their smaller size, which makes them harder to record from intracellularly. Even less is known about betas because it is very difficult to identify a motoneuron as beta while making intracellular recordings. Therefore, most of this section will be concerned with the differences among alpha motoneurons, with some details about the others when available.

3.1. *The size principle or the orderly recruitment of motoneurons*

Since the muscle fibers that constitute most muscles have different contractile properties, the order in which each motor unit is recruited is important for muscle force gradation and metabolic efficiency.

The recruitment of motoneurons depends on numerous factors. First and foremost, like all cells, the membrane of the motoneurons acts like a parallel RC circuit with a resistance and a capacitance. The input resistance of a motoneuron depends on its geometry and its specific membrane resistance, that is the resistance of the membrane per unit area, which is related to the amount of passive channels inserted in the membrane per unit area [136]. Current injected into the neuron through the recording electrode in experimental conditions, or through the opening of synaptic receptors in more physiological conditions, translates into a change of membrane potential proportional to the input resistance of the neuron.

Morphological analyses have shown that all motoneurons do not have the same size. There is approximately a threefold range in soma area [92] among motoneurons and those with the smallest somas have fewer primary dendritic branches and a smaller overall dendritic tree (Fig. 3). Furthermore, there is also a threefold range in

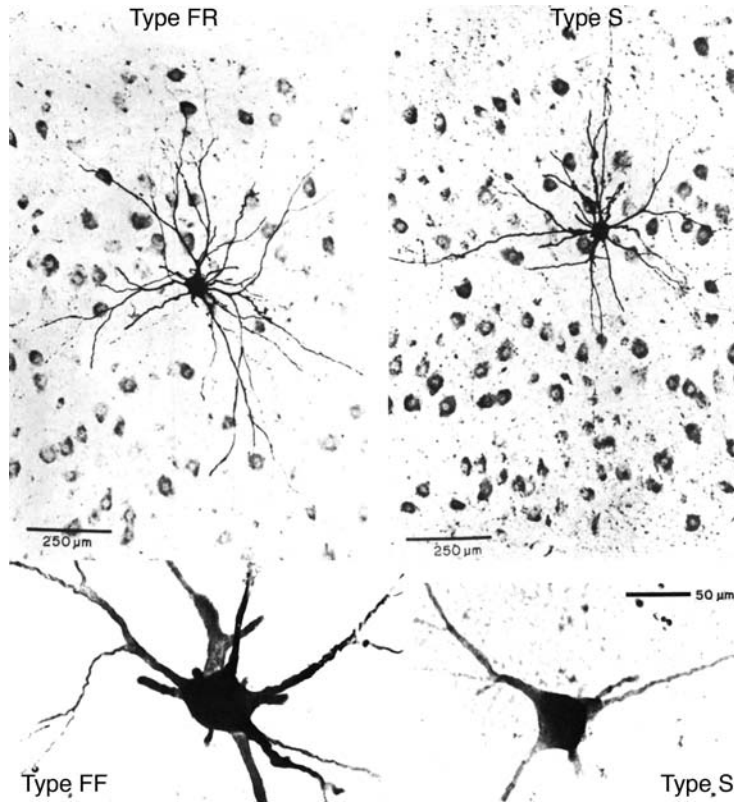


Fig. 3. Size differences among type identified motoneurons. The top two panels illustrate the difference in dendritic arborization between a FR motoneuron from the gastrocnemius pool (left) and an S motoneuron from the soleus pool (right). Adapted from Burke *et al.* [24], with permission. The bottom two panels illustrate the difference in soma size and the number of primary dendritic branches between a FF motoneuron (left) and an S motoneuron (right). Adapted from Burke [23], used with permission from the Am Phys Soc.

specific membrane resistance, such that the smallest motoneurons have the highest resistance per unit area of membrane, while the largest have the smallest specific resistance [58, 59]. The combination of the geometrical and electrical properties yields a 10-fold range in input resistance among motoneurons (although other intrinsic properties must also be considered, see below and [61]). This range seems to be critical for the orderly recruitment motoneurons, as it has been found in cats [151], rats [2] and mice [113].

Henneman *et al.* were the first to argue that an orderly recruitment of motoneurons according to their size (the "size principle", see Ref. [67]) would allow a smooth gradation of the force produced by a motor pool as the "common drive" to the pool increased. This idea was supported by the fact that synaptic inputs are broadly distributed on all the motoneurons of a motor pool. For example, a single Ia afferent was shown to make contact with more than 90% of the motoneurons of the pool [124], which suggests that motoneurons receive a common input. However, the synaptic inputs are not uniformly distributed on motoneurons, and extensive studies by the

Binder laboratory have shown that different pathways can be biased toward smaller or larger motoneurons [65, 87]. Nevertheless, a multitude of studies in humans have shown the size principle to apply in multiple tasks, muscles and movement speeds [41, 53, 85, 143], which fully validate it as a genuine physiological principle.

The functional significance of the size principle was made especially clear when Burke was able to match the electrical properties of motoneurons with the contractile properties of their muscle fibers (see Part I above) [23]. He showed that there are very good correlations between the electrical properties of motoneurons and their physiological type (S, FR and FF, see Part I). As such, the smallest, most excitable motoneurons belong to the S-type, i.e., they innervate fibers that contract slowly and develop little force, but are highly resistant to fatigue. The FR motoneurons have a slightly lower resistance (are less excitable) and innervate fast-contracting, fatigue-resistant fibers. Finally, FF motoneurons are the biggest and the last to be recruited, they innervate fast and powerful muscle fibers that fatigue rapidly. From a metabolic point of view, the size principle allows optimizing the energy consumption of the motor system by first recruiting units that are metabolically efficient, however developing small forces and recruiting units that develop large amounts of force, but with poor efficiency, only when the task requires it [46].

What about gamma motoneurons? Gamma motoneurons are smaller than alphas but their input resistances are in the same range as those of S-type motoneurons suggesting a lower specific membrane resistance [149]. One might think that they would be recruited in the same time as the S-type motoneurons, which would imply that any motor tasks are always accompanied by static and dynamic gamma activation. However, the physiology seems more complex. In some motor tasks, gamma and alpha motoneurons are co-activated but in others they are activated independently (see [74] for a review). Indeed, gamma motoneurons do not share the same common inputs that alphas receive. In particular, gamma motoneurons do not receive monosynaptic Ia inputs [43, 89] (see also one example in [153]). Furthermore, it was shown that gamma dynamic and static motoneurons are differentially driven by descending supra-spinal inputs [74]. Consequently, one can assume that there are dedicated pathways on gamma motoneurons that can activate them specifically depending on the task to be performed.

Burke and Tsairis [29], while examining the muscle fibers that were depleted by the prolonged stimulation of a soleus motoneuron, fortuitously found in their material, one intrafusal bag1 fiber that was depleted in addition to extrafusal fibers. This motoneuron was therefore a beta motoneuron. Interestingly, this motoneuron was receiving monosynaptic Ia EPSPs suggesting that, unlike gamma motoneurons, beta motoneurons share the same synaptic drive as alpha motoneurons [29].

However, motoneurons, like other neurons, in particular are not biophysically passive because, even in the resting state, voltage-dependent channels are open and can influence their responsiveness. In cat spinal motoneurons for example, when one injects a small hyperpolarizing current step through the recording microelectrode, the membrane potential first reaches a peak value in 15−20 ms, then settles at a

smaller (more depolarized) value about 100 ms later [80]. This "sag" in the response is due to the presence of a mixed cationic current activated by hyperpolarization, which is known as the *h*-current (I_h) [121]. The HCN channels mediating this current are partly open at rest and contribute therefore to the input resistance of the motoneuron. When the membrane is hyperpolarized, more channels open, which increases their inward current, and thus depolarizes the membrane in return. Conversely, the HCN channels close when the membrane is depolarized, which lets less inward current in, and thus hyperpolarizes the membrane. As such, it is believed that the function of I_h is to stabilize the resting membrane potential [80].

Yet, the presence of I_h does not invalidate the size principle. Indeed, it was shown very early that the amplitude of the sag, which is roughly proportional to the conductance of the *h*-current, depends on the size of the motoneurons; small motoneurons have little or no sag, while larger motoneurons have a much stronger sag [59, 114]. Therefore, since the open HCN channels decrease the resistance of large motoneurons, the presence of I_h expands the range of input resistance between small and large motoneurons, and thus contributes to the mechanisms underlying the size principle.

The time constant of I_h is slow, however [121], which means that it can only follow slow changes in membrane potentials but not fast changes. As a consequence, the effective input resistance (which is then called "impedance") depends on the frequency of the input. I_h acts as a high pass filter (Fig. 4(b)). Moreover, all cells, because of their parallel RC membrane property, have an impedance that declines at high frequency (Fig. 4(b)). The combination of the low pass filtering by the passive membrane properties and the high-pass filter by I_h creates a band pass filter, i.e., a peak in the impedance curve also known as "membrane resonance" (Fig. 4(b)) [77, 134]. We have shown that a membrane resonance due to I_h exists in cat motoneurons (Fig. 4(a)) [116], as well as in mouse motoneurons (Fig. 4(c)) [113]. Since I_h is stronger in large motoneurons than in small ones, the resonance is also stronger in large motoneurons.

3.2. *Persistent inward currents and the amplification of synaptic inputs*

In addition to I_h, motoneurons possess other currents that can alter their response to synaptic inputs. Indeed, Schwindt and Crill, in the late 1970s described the presence of a negative slope region in the current−voltage relationship of certain motoneurons [141, 142] and hypothesized that this current could amplify and change the time course of synaptic inputs. This current was later called "persistent inward current" (PIC), because it inactivates slowly after it has been opened. This property of the motoneurons was previously unknown because the PIC is highly dependent on the level of neuromodulation [34, 40, 70, 104, 128, 129, 131], but the neuromodulatory pathways are strongly depressed in the commonly used barbiturate anesthetized cat preparations, and the PIC can be directly blocked by the barbiturate

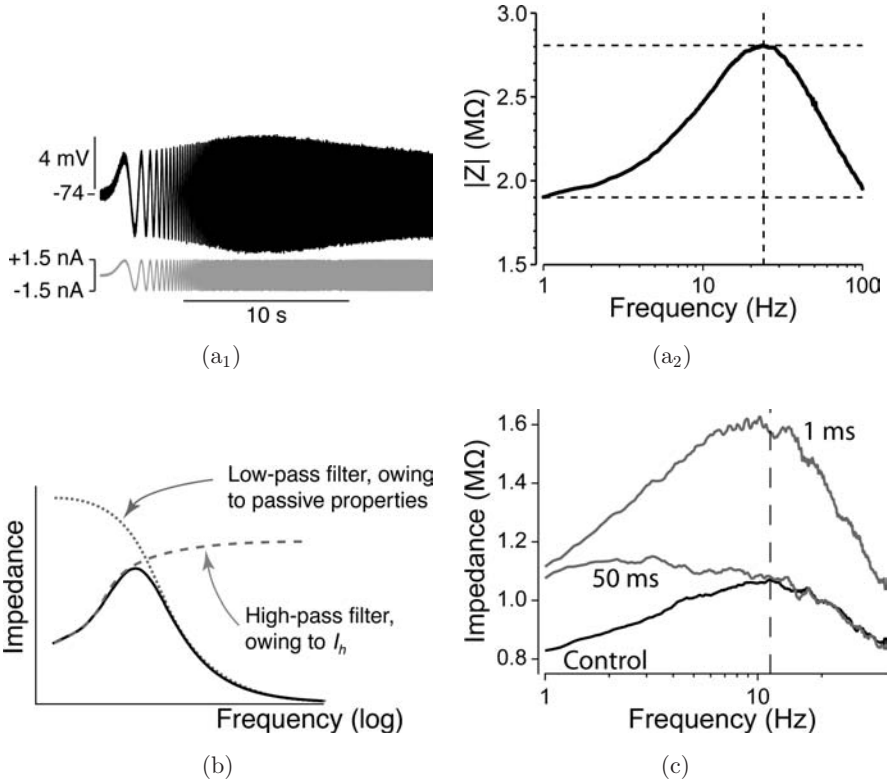


Fig. 4. Resonance properties of motoneurons. (a_1) Response of a mouse motoneuron (top trace) to the injection of a sinusoidal current of increasing frequency (bottom trace). Notice how the response is smaller in response to low frequencies, reaches a peak in the middle of the injected current, and then decreases again when the frequency of the sinusoidal current gets too high. (a_2) Frequency response curve (FRC) of the same motoneuron as in (a_1). The FRC is obtained by plotting the modulus of the complex impedance |Z| versus the frequency. Notice that the curve shows a peak at 24 Hz in this motoneuron. This peak is the signature of the "resonance". Adapted from Manuel *et al.* [113]. (b) Cartoon illustrating how the combination of a low pass filter, due to the passive filtering properties of the membrane, and a high pass filter created by the slow kinetics of Ih, creates a band pass filter, also called "resonance". Adapted from [78]. (c) Effect of the PICs on the resonance. In this experiment, an artificial PIC, either activating quickly (time constant 1 ms) or slowly (time constant 50 ms) was added to a cat motoneuron using dynamic clamp. Notice than in control condition (without added PIC, black trace), this motoneuron showed a resonance at 12 Hz (in cat motoneurons, the resonance frequencies are lower than in mouse motoneurons). Adding a slow activating PIC canceled the resonance by amplifying the low frequencies (grey trace, 50 ms). Adding a fast activating PIC amplified the resonance but amplified preferentially the frequencies around the resonance frequency (top grey trace, 1 ms). Adapted from Manuel *et al.* [116].

anesthetics [57]. The presence of the PIC is readily apparent, however, in decerebrate preparations [7, 8, 40, 70], or by using pharmacological agents reproducing the action of neuromodulators [34, 70, 71, 104, 126].

The presence of the PICs has been found in virtually all types of motoneurons, cat lumbar motoneurons [7, 8, 34, 40, 70, 104], rat lumbar motoneurons [30], rat hypoglossal motoneurons [133, 146], rat sacral motoneurons [9], mouse lumbar

motoneurons [32, 123] and turtle spinal motoneurons [73]. However, the precise molecular substrate of this current is not necessarily the same in all motoneurons. In spinal motoneurons, it was established that a large part of the PIC is mediated by calcium ions, entering the cell through dihydropyridine-sensitive L-type channels [71, 146], most likely Cav1.3 because of their low activation voltage. A significant body of evidence has been accumulated that showed that the location of these channels is dendritic: it was shown that synaptic activity (either excitatory or inhibitory) can change the apparent activation voltage of this current as measured from the soma [8], and it can be activated with a field potential that selectively depolarizes the dendrites [72]. Recently, immuno-labeling, however, demonstrated the presence of these channels on the soma as well as the dendritic tree of motoneurons [65]. Since the dendritic tree is covered with synaptic boutons [25], these channels are in a perfect location to amplify the synaptic inputs to motoneurons. But other channels can also participate in the PIC. For example, in turtle motoneurons, part of the PIC is mediated by a nonselective calcium-activated cationic current (I_{CAN}) [130], while in rat hypoglossal motoneurons, it was argued that the calcium current was carried predominately by Cav2.1 and 2.2 channels [133]. The same group then found that a prolonged PIC can be observed on nucleated patches of membrane, and that this current is blocked by specific agonists of Cav1 channels. They concluded that the PIC in rat hypoglossal motoneurons is mediated by both Cav2 (in the dendrites) and Cav1 (in the soma) channels [127]. Regardless of their exact origin, the calcium PIC (CaPIC) is a slow-activating current that does not (or little) inactivate [32, 109, 141]. It has the potential of producing long tail currents in voltage clamp mode, and "plateau potentials" in current clamp mode.

In addition to the calcium component of the PIC, a substantial portion (about 40−50%) of the PIC is mediated by a persistent sodium current [64, 109, 110, 133]. The molecular origin of this persistent sodium current (I_{NaP}) is less clear. The axon initial segment of motoneurons is very rich in channels Nav1.1 and Nav1.6 [42], but it is unlikely that I_{NaP} is mediated by a specific isoform of the channels. It more likely arises from an alternate activation state of the same channels that generate the spikes [39, 68]. Contrary to CaPIC, this current activates very quickly (with a time constant in the order of the millisecond) [39], and despite not being fully "persistent", it inactivates slowly.

Regardless of their origin, the PICs augment the effective synaptic current that reaches the spike initiation zone of motoneurons [65, 132] amplifying, for example, synaptic inputs elicited by muscle stretches or tendon vibration [8, 86, 105]. Moreover, the fact that motoneurons possess two PICs with very different kinetics allows them to amplify synaptic inputs relevant to their physiological function. We have shown (Fig. 4(b)), through a combination of experiments using dynamic clamp *in vivo* and the study of theoretical models, that I_{NaP} is able to amplify the subthreshold resonance present in motoneurons (see above). In other words, I_{NaP} amplifies preferentially the dynamic components of the inputs (with frequencies close to the resonant frequency) in large — most likely F type — motoneurons,

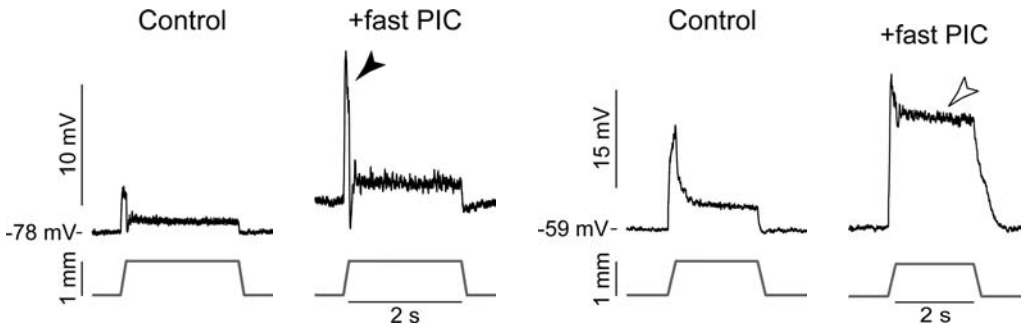


Fig. 5. Differential amplification in resonant and non-resonant motoneurons. (a_1) Response of a *resonant* cat Triceps Surae (TS) motoneuron (top trace) to a ramp-and-hold stretch of the TS (bottom trace). (a_2) Adding, using the dynamic clamp technique, an artificial fast activating PIC (time constant 1 ms) amplifies greatly the dynamic component (filled arrowhead) of the response (top trace) to the same stretch (bottom trace). (b_1) Response of a *non-resonant* (most likely S-type) cat TS motoneuron. (b_2) In this motoneuron, adding a fast activating artificial PIC amplifies all the components of the response, but mostly the static component, by eliciting a plateau potential (empty arrowhead). Adapted from Manuel *et al.* [116].

since they are the one with the strongest resonance (Fig. 5(a)) [116]. On the other hand, because of its slow kinetics, CaPIC amplifies only the low frequency inputs and thereby counteracts the effect of I_h and tend to suppress the resonance (Fig. 4(b)). If CaPIC is strong enough to cancel the resonance, then I_{NaP} amplifies the static inputs. The properties of CaPIC can be modulated by neuromodulatory inputs, in particular by serotonin (5HT), via 5HT2 receptors, and by norepinephrine (NE), via alpha1 receptors [104, 108, 131]. Likewise, I_{NaP} is also under monoaminergic neuromodulation [63]. Provided that the modulation of CaPIC and I_{NaP} is done through different subtypes, or subpopulations, of receptors, it is interesting to imagine that the motor system might be able to modulate independently the relative strength of CaPIC and I_{NaP}. This would allow to adjust the amplification of dynamic and static synaptic inputs depending on the task [116]. In non-resonant motoneurons however (i.e., S-type motoneurons), we have shown that both PICs amplify the static component of the inputs (Fig. 5(b)). This effect is further accentuated by the fact that the properties of the PIC (especially CaPIC) are different between S and F motoneurons. Lee and Heckman [102] have indeed shown that, in putative S motoneurons, the PIC activates at a lower voltage, and tend to persist longer, showing a marked hysteresis between the upward and downward portion of a voltage ramp, than in putative F motoneurons. These differences translate into distinct responses in the two populations of motoneurons. When activated in F motoneurons, the PIC induces a steady depolarization ("plateau potential") but cannot sustain it for more than 1−2 s. By contrast, in S motoneurons, the plateau potential always last longer than 3 s [103]. These long-lasting plateau potentials might be necessary for the function of these small motoneurons that are heavily implicated in postural task where a steady firing is required, as

opposed to larger motoneurons that would be recruited more transiently. There are indeed evidences showing that extensor motoneurons, which play a critical role in postural tasks, and during the stance phase of locomotion, have a greater capacity for self-sustained firing thank to a plateau potential caused by the activation of the PICs than flexor motoneurons (see Sec. 3.3.3) [38, 70].

3.3. *The firing properties of motoneurons*

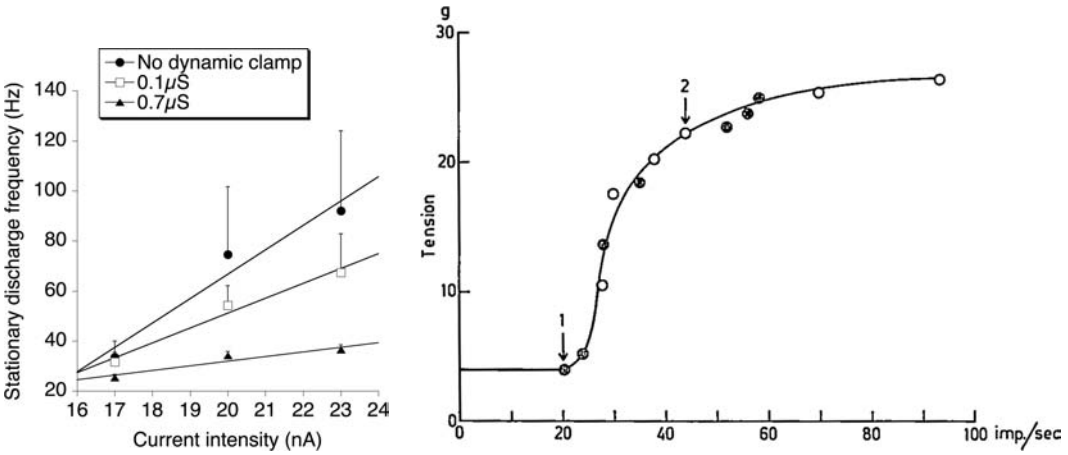
With the discovery of PICs and its continued study in more and more species, our understanding of the firing properties of motoneurons has dramatically evolved during the past two decades. We will first review the firing properties that were originally described in motoneurons of cats deeply anesthetized with barbiturates, and then how this view was challenged by recent studies.

3.3.1. "*Speed matching*" *in cat motor units*

Once synaptic input has sufficiently depolarized the motoneuron, like in any other excitable cell, an action potential is generated. This action potential is followed by a phase of hyperpolarization, called the "after hyperpolarization" (AHP) [35], which has been extensively studied since the very first intracellular recordings of motoneurons. It was shown to be mediated by channels permeable to potassium [36]. These channels, contrary to those discussed so far, are not voltage dependent but are opened by intracellular calcium [121, 147] which enters the cell via high threshold, voltage-sensitive channels [146, 147]. The channels mediating the AHP were identified as "SK" channels by their sensitivity to the bee venom apamin [147, 152]. Along with the difference in input resistance (or size), the AHP characteristics were the first to be shown to be different in the different types of motoneurons. Eccles *et al.* [44] already showed that the motoneurons innervating slow contracting muscles have generally a longer AHP than the motoneurons supplying fast muscles, which has subsequently been confirmed by many groups [58, 151]. It was suggested that the strong sag in large motoneurons could be responsible for this difference [60], but the difference in duration persists when one takes care to select motoneurons with an h-current too slow to affect the kinetics of the AHP [114]. Today, it is agreed that the time course of the AHP is due to the speed of buffering of internal calcium [139], which might therefore be different between S and F motoneurons, either because of their size difference, or because of a difference in the expression of calcium buffers. Similarly, the amplitude of the AHP depends on the physiological type of the motoneuron: FF motoneurons have a shallower AHP than S motoneurons [151], but we have shown that this difference is due to the difference in input conductance because the AHP conductance recruited by a spike is not different in large versus small motoneurons [114].

The differences in the AHP duration in different types of motoneurons play an important functional role, a long lasting AHP limits the firing to low frequencies [92]. The extensive studies by Kernell's group have shown that, at the minimal

amount of current that elicits repetitive firing in spinal motoneurons of deeply anesthetized cats, the period between two spikes (the minimum firing frequency) is, in fact, equal to the duration of their AHP [90]: S motoneurons have therefore a lower minimal firing rate than FF motoneurons. As the intensity of the injected current is increased, the frequency increases in a linear fashion ("primary range"), up to a limit that is also dependent on the duration of the AHP [90]. The slope of the linear relationship between the current and the discharge frequency in the primary range is essentially controlled by the AHP, as we have shown both theoretically and experimentally (Fig. 6(a)) [114, 115]. In each cat motoneuron, the AHP duration is precisely adapted to the twitch duration of the muscle fibers that the motoneuron innervates ("speed matching") [92]. As such the AHP allows the precise adaptation of the discharge to the contractile properties of the muscle fibers. At recruitment, the firing frequency is lower in S motor units that have a longer lasting contraction, and faster in FF motor units that contract quickly. The minimal firing frequency thus corresponds to the frequency at which twitches just start to sum, and the force produced by the motor unit is small [92]. As the amount of excitation increases, the firing frequency increases linearly, which in turn allows the force to be finely gradated (Fig. 6(b)). The maximal frequency at the end of the primary range is also controlled by the AHP in such a way that it corresponds to the frequency for which the twitches are fully fused and the force reaches its maximum ("tetanic fusion frequency") [92]. The AHP therefore controls the rate of firing of motoneurons



(a) (b)

Fig. 6. Force gradation in the primary range, and control of the gain by the AHP. (a) In a motoneuron on which the AHP was dramatically reduced by the injection of the calcium chelator BAPTA, the gain was initially very high (about ten times the normal gain). Adding an artificial AHP with the dynamic clamp technique reduced the gain of the motoneuron. From Manuel *et al.* [115]. (b) Plot of the isometric force of a gastrocnemius motor unit vs. the discharge frequency of its motoneuron. Arrow 1 points to the minimal firing frequency of the motoneuron, while arrow 2 points to the maximal firing rate reached at the end of the primary range. Note that more than 80% of the force of this motor unit is recruited during the primary range. Reproduced, with permission, from Kernell *et al.* [91].

(i.e., the "gain" of the motoneuron) and by extension the gradation of motor unit force. The AHP is clearly a critical element of a motoneuron physiology. The AHP current is under tight neuromodulatory control, by 5HT and NE [63, 104, 108], but mostly by cholinergic C terminals that colocalize closely with SK channels [125]. Neuromodulation of the AHP has deep consequences. For instance, it was shown that during locomotion and the scratch reflex, the AHP is strongly reduced and the firing gain of the motoneuron is strongly increased [22]. The AHP plays the double role of adapting the discharge characteristics in the basal state so as to ensure a smooth gradation of the force, but also being a control variable that allows a dramatic increase of the gain and rate of force recruitment in any conditions where the movement to be performed requires it.

Very few gamma motoneurons have been intracellularly recorded for technical reasons [43, 89, 148]. Recordings of gamma motoneurons revealed that they are able to discharge at very high frequency (>200 Hz) and with a very high gain (20−60 Hz/nA), most likely because of a very shallow and short-duration AHP [74, 89, 148]. This fits to the properties of nuclear chain fibers, which display a very short contraction time and a high tetanic fusion frequency (see Sec. 2), suggesting that the discharge properties of gamma motoneurons are, in the same way as in alpha motoneurons, adapted to the contractile properties of their muscle fibers. However, despite the fact that bag1 fibers are slower than the nuclear chain fibers [16], gamma motoneurons with low gain and low firing frequencies have not been recorded. This might well be because of the small number of gamma motoneurons studied so far.

3.3.2. *Firing properties of mouse and rat motoneurons*

At least in alpha motoneurons, the AHP is not, however, the sole current that affects the repetitive discharge of motoneurons. The sodium persistent inward current, in particular, was shown to be critical for the initiation of each spike during a repetitive discharge, as it activates a few millivolts below the spiking threshold and provides an initial acceleration of the voltage trajectory, which allows the transient sodium channels to escape their inactivated state [64, 100, 106]. The voltage threshold of motoneurons does not depend on their physiological type [58] and no obvious differences have been observed across species. However, we have shown that, in mouse motoneurons, the fast-activating sodium current responsible for the spike generation is likely endowed with a very slow inactivation process, which creates a state of relative hypo-excitability [79], delays spike initiation, and induces subthreshold oscillations [113]. The presence of these oscillations creates a new regime of firing before the classical primary range, that we dubbed the "subprimary range". In this range, contrary to the situation in cat motoneurons, inter-spike intervals can be longer than the duration of the AHP, and the number of oscillations at the end of the AHP essentially controls the period. Surprisingly, we have shown that, in this small animal, most of the motor unit force is recruited during the subprimary range and not in the primary range as in cats [112]. This new mode of

recruitment of force might be functionally important for small animals like rodents, as a subprimary range has also been recently described in rat lumbar motoneurons [145]. Note that, however, these results do not invalidate the "speed matching" of motoneurons and muscle fibers. In mouse as well as in rat motoneurons, the AHP duration displays systematic variations with the input resistance and the conduction velocities of the motoneurons [2, 112]. It seems instead that the "match" between the AHP duration and the twitch duration is done in such a way that it allows a substantial proportion of the force to be recruited during the subprimary range in rodents [112]. The AHP is likely to play an active role in controlling the subthreshold oscillations and thereby the subprimary firing range. The larger and longer AHP of cat motoneurons is more efficient at deinactivating the sodium channels, and therefore allows a larger proportion of channels to be activated when the membrane reaches threshold. Indeed, we have shown that the subthreshold oscillations disappear in mouse motoneurons when one artificially increases the amplitude of the AHP using the dynamic clamp technique, or by adding some extra artificial persistent sodium current [79].

3.3.3. *Impact of PICs on the discharge*

Finally, it was shown, almost since their initial discovery, that PICs, and in particular CaPIC, can have a strong impact on the discharge properties of motoneurons. In their strongest manifestation, PICs are able to produce long lasting plateau potentials that can produce a "self-sustained firing" [34, 40, 70, 72, 73, 103]. This property is also called "membrane bistability" (Fig. 7(a)), as motoneurons can exist in two stable states: quiescent (not discharging), or firing continuously without the need to receive a sustained synaptic activation. However, as noted earlier, this property is not found in any type of motoneurons. S-type motoneurons, especially those innervating extensor muscles [38], seem more prone to exhibit a full bistability, while FF-type motoneurons only display a partial bistability; even though they exhibit self-sustained firing, it tends to stop on its own after a few seconds [103]. Even when they are not strong enough to turn the membrane bistable, the PICs can cause an acceleration of the discharge, and, in response to a triangular ramp of current for example, a counterclockwise hysteresis on the current−frequency relationship (Figs. 7(b) and 7(c)) [8, 9, 34]. It is not clear if and how these phenomena (bistability and counterclockwise hysteresis) are involved in the physiological control of motoneurons in normal humans (see next section), but a substantial body of evidence exists that shows that "abnormal" PICs can be implicated in pathologies like amyotrophic lateral sclerosis (ALS) [48, 122, 135] and spasticity after spinal lesion [9, 109, 110]. In the latter case, for example, Bennett's group has elegantly demonstrated that, two months after complete spinal transection, the loss of serotoninergic innervation from the brainstem on motoneurons causes a transformation of the 5HT2 receptors, which become constitutively active [54] and thus cause a pathological overexpression of the PICs.

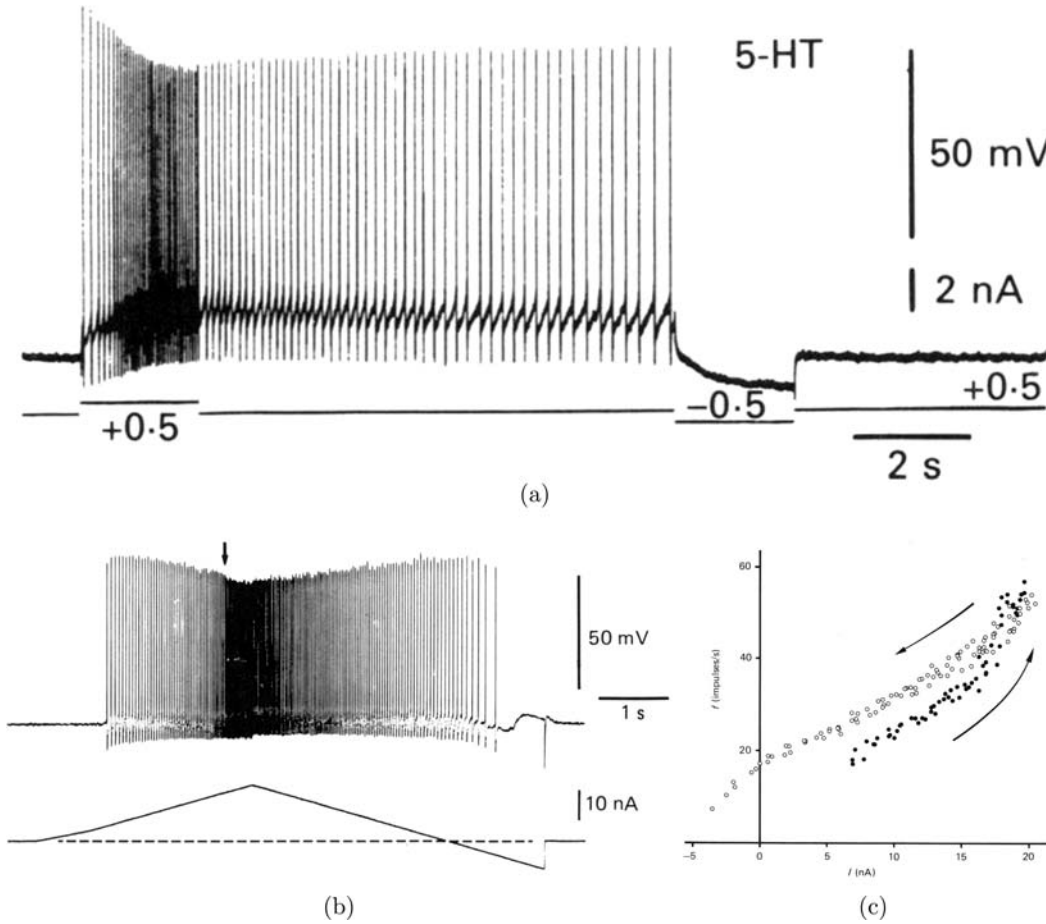


Fig. 7. Impact of the PICs on the discharge of motoneurons. (a) Membrane bistability in a turtle motoneuron. In this experiment, the PICs of a turtle motoneuron recorded *in vitro* were revealed by the addition of serotonin (5-HT) to the recording chamber. In these conditions, a depolarizing pulse of current (bottom trace) initiated the discharge (top trace), which accelerated during the pulse. Once the pulse was turned off, a self-sustained discharge is apparent, and it required a hyperpolarizing pulse of current to turn it off. From Hounsgaard and Kiehn [71], with permission. (b) Recording from a cat lumbar motoneuron (top trace) injected with 5-HT intravenously, in response to a ramp of current (bottom trace). The arrow points to an acceleration of the discharge on the ascending ramp. Note that the discharge last much longer on the descending ramp than on the ascending ramp, and that a negative amount of current is required to stop the discharge. (c) Frequency−current curve from the motoneuron in (b). The curve shows a clear counterclockwise hysteresis between the upward ramp (black dots) and the downward ramp (white dots). From Hounsgaard *et al.* [70], with permission.

3.4. *PICs in human motoneurons and some consequences for human neurophysiological studies*

As discussed above, in animals, PICs proved to play three important roles in spinal motoneurons: (1) they contribute to maintain a repetitive discharge during prolonged inputs (I_{NaP}), (2) they amplify synaptic inputs (I_{NaP}, CaPIC) and (3) they alter the shape of the current−frequency relationship (CaPIC). These effects largely depend on

the amount of 5-HT neuromodulation. It is likely that PICs induce similar actions in human spinal motoneurons. However, it is quite difficult to obtain and interpret the evidence of any such actions in human motoneurons (see [66] for a review).

The first evidence was given by the observation in some motor units of a prolonged EMG activity that continues after a short period of tendon vibration [94]. The prolongation of the motoneuron discharge was interpreted as resulting from a recruitment of a PIC by the tonic Ia EPSPs elicited by the spindle vibrations [94]. The PIC induces a self-sustained discharge that outlasts the vibration period [55, 94]. Paired motor-unit recordings provided a further argument in favor of PIC activation [55, 94]. The firing activity of a low threshold motor unit is used as a reflection of the synaptic drive. As the synaptic drive is largely common over the population of alpha motoneurons, any prolongation of the firing activity in the higher threshold motor unit suggests that this prolongation might be due to the activation of a persistent inward current in the motoneuron. Gorassini *et al.* [55] have used this technique to determine the relative strength of the PIC current during slow triangular movements. As a result of the PIC activation, the discharge of the motor units displays a counterclockwise hysteresis during triangular movements. Recently, Fuglevand has showed at the Paris Motoneuron Meeting (http://motoneuron2010.parisdescartes.fr/) that the hysteretic pattern of discharge during triangular forces tends to become linear when a cutaneous stimulation is applied during the contraction. The most likely explanation is that PIC was disengaged by the strong inhibition elicited by the cutaneous afferents. This result suggests again that PICs may shape the activity of human motoneurons.

Since PICs are present in human motoneurons, one might thereby wonder whether they influence the motor output during the tests of motoneuron excitability (H-reflexes and transcortical magnetic stimulation (TMS)) that are classically used in human neurophysiological studies [31]. Lessons from the animal experiments reviewed here prompted us to make the following suggestions. The excitatory potentials evoked in motoneurons during these tests might be amplified by the PICs, depending on their time course, thereby increasing the probability of reaching the threshold for discharge. Since the H-reflex is achieved by applying a single electrical shock on the nerve, it is very likely that the stimulation-induced Ia EPSPs are much too brief (a few milliseconds) to engage CaPIC. On the other hand, however, I_{NaP} might be able to amplify brief EPSPs [86, 116]. Furthermore, it is likely that the EPSPs amplification by I_{NaP} would be more important in the motoneurons innervating fast-contracting motor units that display a marked resonance than in those innervating the slow contracting motor units that hardly display any resonance (see above) [116]. Motoneurons innervating the fast-contracting motor units will then reach their firing threshold with a higher probability when the neuromodulatory state is such that I_{NaP} is strongly expressed. In conditions of strong neuromodulation, and assuming that the size principle is respected during the H-reflex, Ia input larger than the one necessary to recruit S-type motoneurons would recruit more F-type motoneurons. However, as the H-reflex is often tested in the soleus

muscle, composed nearly entirely of S-type motor units, such a consideration may not apply in this instance. In the same line, the impact of PICs in motoneurons during TMS depends on the shape of post-synaptic potentials induced by the descending inputs. Excitatory potentials on motoneurons evoked by TMS may be longer than those evoked by the H-reflex method but they do not exceed 10 ms [138]. This is due to the fact that, even in response to a single TMS shock, the cortical output is more complex than a single volley. Furthermore, differences in the conduction velocities in descending axons of cortical cells might result in further desynchronization of the command to motoneurons. However, the duration of excitatory inputs on motoneurons in response to TMS stimulation is still too short to substantially engage CaPIC [116]. I_{NaP} is likely to be the only one PIC active in motoneurons during TMS. Similarly as with the H-reflex, TMS might tend to recruit more F motoneurons in circumstances where the neuromodulation allows a significant I_{NaP} expression.

In conclusion, PICs have been inferred to exist in human motoneurons. Some caution must therefore be taken in interpreting the results from classical neurophysiological studies that, in part, depend on motoneuron excitability. It would be very useful to find methods to determine the "neuromodulatory state" of the subject in different motor tasks since any changes on this state can modify I_{NaP} [63], CaPIC [105], and the resonance acuity of motoneurons by changing I_h [95].

4. Conclusion: A Wide Functional Diversity of Spinal Motoneurons

Since Sherrington, our conception of the final common pathway has considerably evolved. Meticulous studies have shown that motoneurons innervate a multitude of muscle targets in a well organized plan, resulting in a heterogeneous functional population of motoneurons. Ordinary (extrafusal) muscle fibers are differentiated in three main types with contrasting physiological properties. Furthermore, each alpha motoneuron innervates muscle fibers that are all of the same type. It is then legitimate to consider that there exist three corresponding functional types of alpha motoneurons. Intrafusal muscle fibers differentiate in fibers that supply the dynamic (bag1 fiber) and the static (bag2 fiber and chain fibers) sensitivity of spindle endings. A gamma motoneuron elicits a dynamic or a static action depending on which group of intrafusal fibers it targets. Importantly, a substantial fraction of motoneurons (beta motoneurons) innervate both extrafusal and intrafusal fibers. Remarkably, there is a link between their intrafusal and extrafusal innervation that depends on the action, dynamic or static, they elicit on spindle endings.

What is more, the electrical properties of each motoneuron are precisely adapted to the contractile properties of their targets. Each type of muscle fiber (slow contracting or type I, fast contracting fatigue resistant or type IIA, fast fatigable or type IIB, intrafusal bag fibers and chain fibers) has indeed very different duration of contraction. Yet, despite the fact that all motoneurons share more or less the same set of voltage-dependent currents, the precise characteristics of these currents are

regulated so that the motoneurons can activate its target in the most efficacious way possible. The size difference among alpha motoneuron guaranties an energy efficient way to generate force. Furthermore, interactions between I_h, a fast I_{NaP} and a slow CaPIC (all of which can be regulated by neuromodulatory inputs) allow the differential amplification of the inputs that are the most relevant to the physiology of the motoneurons (static inputs in S motoneurons, dynamic inputs in F motoneurons). Finally, the AHP regulates the firing frequency range so as to guaranty that the firing will not be too rapid or too slow to generate the required muscle force.

It is obvious that both the innervation pattern of the different types of motoneurons and the membrane receptors and ionic channels that determine their electrical properties require a very precise control during development by sophisticated molecular signals. Only a few of these signals are known so far (for a review see [88]) and the search for the signals that guide a given axon towards its specific target remains an important issue. It is very likely that the fate of each motoneuron within a pool is to some extend determined quite early during development and recent works have uncovered some transcriptional factors or molecular signatures specific of a given motoneuron type [88]. However, it is still unclear whether the properties of motoneurons and muscle fibers are predetermined and each motoneuron seeks out compatible muscle fibers, or if, on the contrary, the properties of motoneurons and muscle fibers co-mature during development to obtain a properly adapted functional motor unit. The elucidation of these mechanisms would considerably advance on our understanding of the physiology of the motor system. It would also have promising therapeutic application for the treatment of diseases like ALS, which affect specific populations of motoneurons and not the others.

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LINEAR VISUOMOTOR TRANSFORMATIONS IN MIDBRAIN SUPERIOR COLLICULUS CONTROL SACCADIC EYE-MOVEMENTS

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It is well established that a localized population of neurons in the motor map of the midbrain superior colliculus (SC) drives a saccadic eye-head gaze shift. However, there is controversy as to how the brainstem saccade burst generators decode the SC activity. We focus on eye-movement generation by comparing two competing schemes from the recent literature that are both supported by neurophysiological evidence: the vector-averaging scheme versus the vector summation model. Whereas the former contains at least four nonlinearities to explain visuomotor planning and saccade execution, the latter relies predominantly on linear operations. We have demonstrated that the summation model accounts for the nonlinear main sequence of saccade kinematics, and predicted that this results from a spatial gradient in temporal burst profiles of SC cells: rostral cells have higher peak-firing rates and shorter burst durations than caudal cells. Yet, the number of spikes in their saccade-related bursts is identical. In contrast, the averaging model does not predict such activity profiles. We now also show that by incorporating the concept of predictive remapping in the spatial updating of saccade sequences, the phenomenon of target averaging in double-stimulation experiments, and the occurrence of goal-directed, but highly curved saccades in the double-step paradigm, can all be explained by the same linear summation mechanism. We argue that the linear model is more in line with neurophysiological data, while relying on fewer ad-hoc assumptions than the nonlinear vector-averaging scheme.

Keywords: Saccades; superior colliculus; main sequence; linearity; nonlinearity; models; monkey; population coding; optimal control.

1. Introduction

1.1. *Saccade kinematics: A nonlinear system*

Saccadic eye movements ("saccades", for short) are the rapid, conjugate displacements of the eyes that have the function to redirect the fovea as fast and as accurately as possible to a peripheral target of interest. Visually evoked saccades have remarkably stereotyped movement characteristics: their trajectories are virtually

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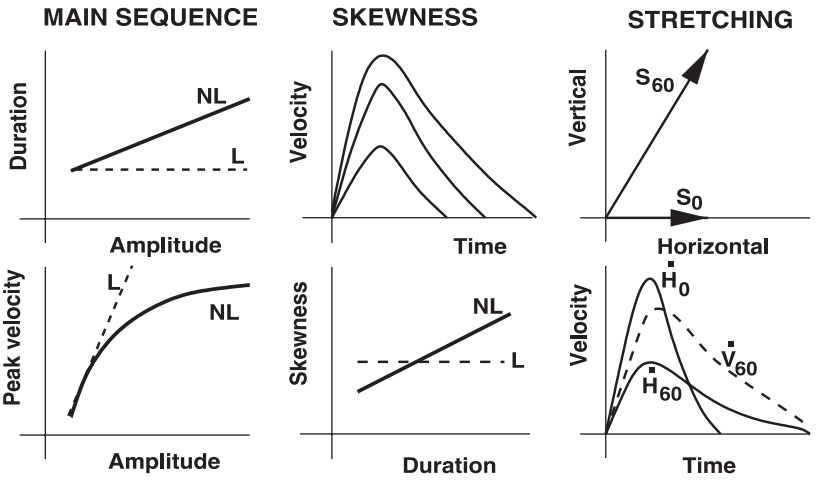


Fig. 1. Properties of saccade kinematics. (a) The main sequence betrays a nonlinearity (NL), as for a linear system (L) saccade duration would be constant, and peak eye velocity should increase linearly with amplitude. (b) The shape of velocity profiles depends on saccade duration: large saccades are more skewed than small saccades. (c) Component stretching of oblique saccades: their horizontal and vertical velocity components have the same shape and duration (adapted from [48]).

straight, there is a consistent straight-line relationship between movement duration and saccade amplitude, the saccade acceleration time is nearly constant for all saccades, and the relationship between peak eye velocity versus saccade amplitude is described by a saturating function (Figs. 1(a) and 1(b)).

It was already recognized by Westheimer [56] that these kinematic relations, known in the literature as the "*main sequence*" of saccades [1], reveal a *nonlinearity* in the saccadic system (Fig. 1(a), "NL"). Indeed, for a linear system ("L"), the movement characteristics should scale linearly with movement amplitude: mathematically, if $s_1(t)$ is the unitary saccade for a target step of one deg, then $\lambda \cdot s_1(t)$ should be the saccade trajectory for an amplitude of λ deg. In other words, the saccade duration should be the same for all saccades, the shape of their velocity profiles should be identical, and their peak eye velocities would have to increase linearly with amplitude, λ. It is important to realize that the saccade kinematic nonlinearity is not due to extraocular plant mechanics, as the pulse-step activity profiles of the extraocular motoneurons fully reflect the main sequence properties: the pulse duration matches the saccade duration, and the peak activity of the pulse saturates for large saccade amplitudes.

Oblique saccades follow the main sequence characteristics, and because the trajectories of saccades in two dimensions are approximately straight, the velocity profiles of the horizontal, $\dot{h}(t)$, and vertical, $\dot{v}(t)$, components are scaled versions of each other: $\dot{v}(t) = \tan(\Phi) \cdot \dot{h}(t)$, with Φ the vectorial saccade direction [7, 45]. This property thus defines another nonlinearity, because the peak velocity (and duration) of a given horizontal (or vertical) movement component is not fixed, but varies with

the saccade direction (Fig. 1(c)). For example, a 10-deg horizontal saccade ($\vec{s}_0$) may reach a peak velocity of 350 deg/s, and a duration of, say, 45 ms. An oblique saccade in a direction of $\Phi = 60$ deg with the same horizontal displacement ($\vec{s}_{60}$ in Fig. 1(c)) has an amplitude of 20 deg. According to the main sequence, its vectorial peak velocity, $\dot{v}_{\mathrm{VEC}} = \sqrt{\dot{h}^2 + \dot{v}^2}$, will be about 550 deg/s (i.e., less than twice the peak velocity of a 10-deg saccade), and a duration of 75 ms. The 10-deg horizontal component of this oblique saccade then also has a duration of 75 ms, and a reduced peak velocity of only 275 deg/s (halve the velocity of the total vector). This phenomenon is called "component stretching", as movement components are stretched in time to match the duration of the movement vector (Fig. 1(c)).

Nearly every neural model of the saccadic system assumes that the main sequence properties result from nonlinear local feedback circuits in the brainstem, in which so-called medium lead burst cells in the paramedian pontine reticular formation (PPRF, for horizontal saccades; [20, 24, 43]) and in the rostral interstitial nucleus of the mesencephalic longitudinal fasciculus (riMLF, for vertical-torsional saccades [21]; we ignore torsion in this paper) are thought to be driven by horizontal and vertical dynamic motor error signals, respectively (see Fig. 3).

The brainstem burst cells transform the dynamic motor-error signal into the component's eye-velocity output, a process known as pulse (or burst) generation. The far majority of saccade models assume that the input−output characteristics of the pulse generators follow a saturating nonlinearity that mimics the amplitude−peak velocity relation of Fig. 1(a) (e.g., [36, 45]). The underlying idea is that the presumed high-gain burst cells are driven into saturation for almost all saccades, and that as a result of neural fatigue this affects the shape of their instantaneous input−output relationship. Fatigue then accounts for the skewness of saccade velocity profiles: a short, nearly constant acceleration toward peak eye velocity in about 20−25 ms, followed by a saccade−amplitude-dependent deceleration phase until the saccade has ended [49]. As a result, small saccades have nearly symmetrical velocity profiles (roughly equal acceleration and deceleration phases), but large saccades are positively skewed as the deceleration phase outlasts acceleration.

However, the presumed nonlinearities of the local feedback loops lead to nasty problems for the instantaneous coupling of horizontal and vertical movement components of oblique saccades (Fig. 1(c); e.g., [17, 27, 37, 45]). Given the complications to produce straight oblique saccades, we believe the question is justified why the pulse generators would contain a saturating nonlinearity in the first place.

We argue that there is surprisingly little data to support the commonly held assumption that the input−output characteristic of the pulse generator underlies the main sequence nonlinearity. A critical problem is that the true nature and dynamics of the input signals to the brainstem burst cells (presumed to be dynamic motor error) are in fact unknown, as single-cell recordings only

provide information about the cell's output (which is strongly related to the eye velocity component). Furthermore, we believe it is unlikely that the nonlinearity of saccade kinematics would reflect a mere passive saturation, or neural fatigue, for the following reasons:

First, behavioral data have shown that the much slower saccades to remembered targets in darkness obey their own nonlinear main sequence, in which the velocity asymptote is considerably lower than for visually triggered saccades [37].

Second, neurons in the abducens and oculomotor nuclei reach firing rates that are as high as those of the brainstem burst neurons. Yet, models of the saccadic system invariantly employ linear transfer characteristics to describe these other types of neurons.

Third, even though oculomotor neurons do have nonlinear characteristics (they essentially behave as rectifiers, since they are recruited beyond a threshold), it is thought that the output of the total neuronal population varies approximately linearly with changes in eye position across the oculomotor range [44]. Taken together, although the concept of a nonlinear brainstem burst generator is a central dogma in saccadic system theories, its experimental evidence is not compelling. Further, it is questionable whether nonlinearities at the single-cell level inevitably cause nonlinearities at the population level of the brainstem burst generators (e.g., [41, 44]).

1.2. *The midbrain-brainstem saccade generator*

It is well established that a population of neurons in the motor map of the midbrain superior colliculus (SC) encodes the coordinates (amplitude and direction) of an upcoming saccadic eye movement (Fig. 2). The idea is that since each cell in the SC prefers a particular movement vector (quantified by its movement field; Figs. 2(a)–2(c)), the total saccade is determined by combining the weighted contributions from all recruited cells. The weights are thought to depend on two factors: (i) the fixed connection strength of a cell with the horizontal and vertical burst generators, which is completely determined by its location in the SC motor map, and (ii) the cell's activity, which depends on the intended saccade vector.

However, there is controversy as to how the SC population activity is eventually decoded/weighted by the brainstem. In particular, the discussion boils down to the question whether saccade-related SC activity also carries information regarding the eye movement trajectory and its kinematics (a *motor theory* of the SC), or whether the temporal details and levels of the activity patterns are immaterial, as the population merely encodes the saccade vector (the "*goal theory*" of the SC). We here compare two competing schemes from the recent literature that well illustrate this controversy, and are both supported by neurophysiological evidence: the *vector averaging* scheme (proponent of the goal theory) versus the *vector summation* model (proponent of the motor theory), respectively. We will first describe these two models in some detail, to better enable a quantitative comparison.

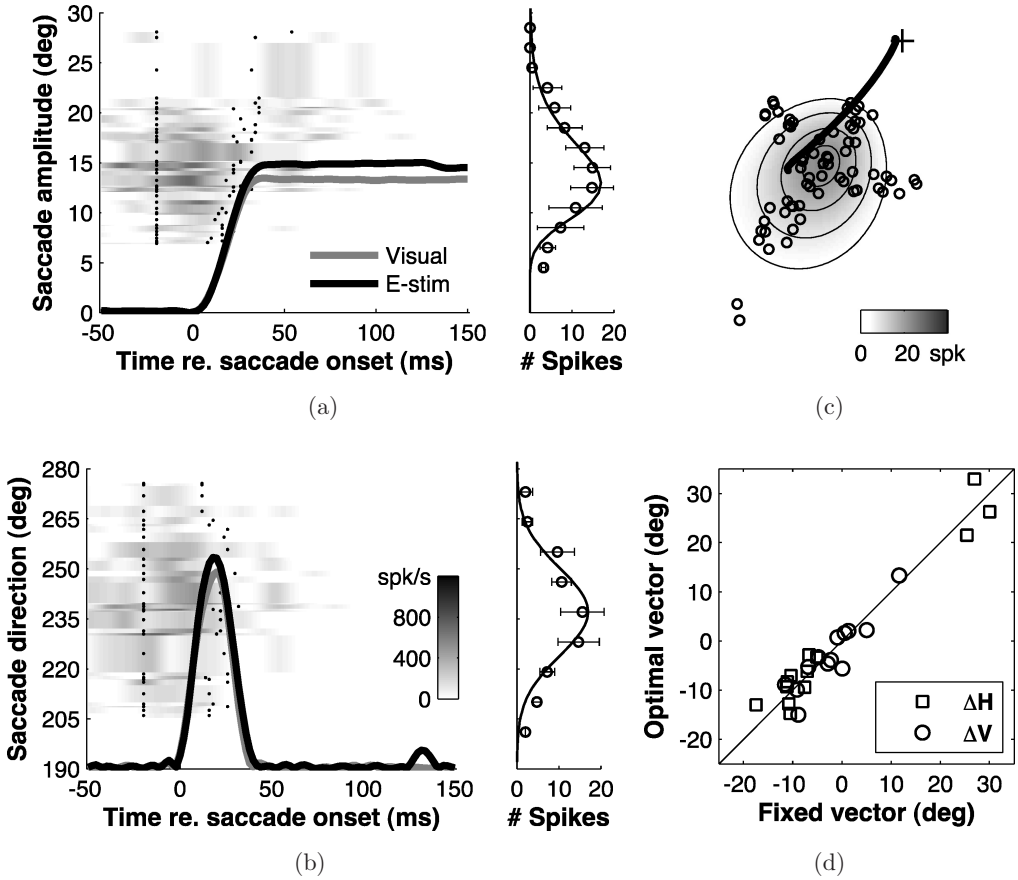


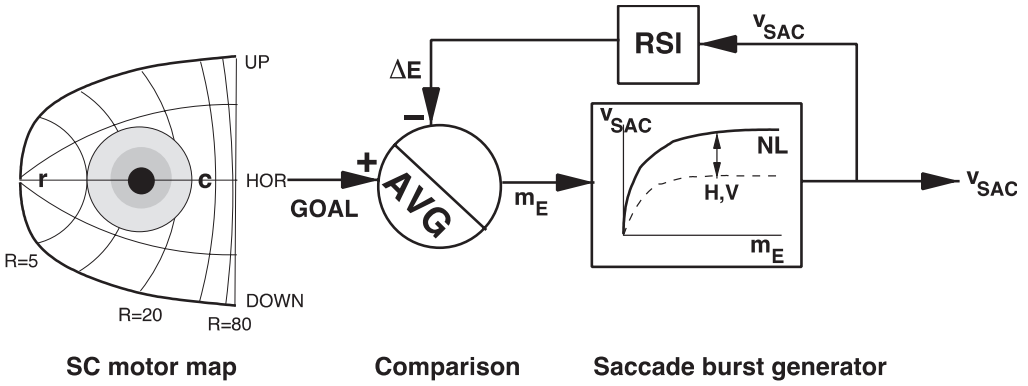
Fig. 2. Single-unit movement field and microstimulation in monkey superior colliculus. (a–c) Neural activity (in gray scale) for saccades into the cell's movement field (optimum at $[R, \Phi] = [15, 240]$ deg). (a) Amplitude scan. Gray eye movement trace: visual saccade into movement field center; black: saccade evoked by microstimulation at 20 μA (500 Hz; cathodic pulses). Inset right: number of spikes (with sd) as function of amplitude. (b) Direction scan through the movement field, with eye velocity traces for visual (gray) and electrical microstimulation (black). Inset: number of spikes as function of direction. (c) Movement field. Dots: visual saccades, selected for amplitude and direction scans. Black trace: stimulation-evoked saccade. (d) Stimulation saccades and optimal visual saccades for 14 different sites. Stimulation evokes a saccade into the center of the movement field of recorded cells near the stimulation electrode.

1.2.1. *Vector averaging*

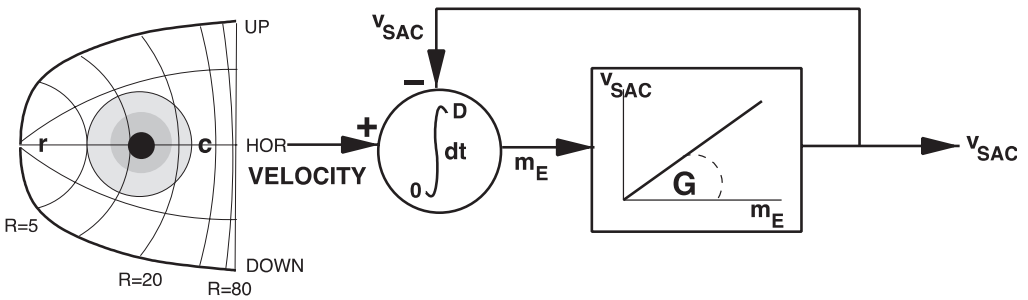
According to the vector-averaging hypothesis, the SC output specifies a dynamic oculocentric goal, which is computed by averaging all cell contributions from the recruited population by:

$$\vec{S}_{\mathrm{AVG}}(t) = \frac{\sum_{n=1}^{N_A} f_n(t) \cdot \vec{R}_n}{\sum_{n=1}^{N_A} f_n(t)}. \tag{1.1}$$

with N_A the total number of active cells, $f_n(t)$ the instantaneous firing rate of cell n, and $\vec{R}_n$ the fixed movement vector corresponding to the locus of cell n in the motor



(a)



(b)

Fig. 3. The SC-brainstem saccade controller. The SC motor map is logarithmically compressed in the rostral (r)−caudal (c) direction for saccade amplitude (shown from $R = 5$ to $R = 80$ deg), and is roughly linear for saccade direction (medial, upward saccades, to lateral, for downward saccades). The brainstem (right) contains dynamic feedback loops to generate horizontal/vertical saccade component velocities for clarity, only one burst generator is shown. (a) Nonlinear vector-averaging model (after [55]). RSI: resettable integrator. AVG: vector averaging of SC output. ΔE: current eye displacement. NL: dynamic brainstem nonlinearity. H, V: gain modulation of horizontal/vertical burst generators during oblique saccades; the fatigue mechanism is not included. (b) Linear vector-summation model (after [15]). D: saccade duration; v_{SAC}: current saccade velocity; G: gain of linear burst generator.

map [23, 30, 55]. Equation (1.1) effectively computes the center-of-gravity of the population in motor coordinates. The saccadic burst generator is then driven by dynamic eye motor error, $m_E(t)$, which is the difference between the SC goal (which is reached almost instantaneously) and the current eye displacement; the latter is obtained by integrating the burst-generator's velocity output (Fig. 3(a)). To account for the nonlinear saccade main sequence [1, 56], the burst generator's nonlinear input−output characteristic is usually written as:

$$\vec{v}_{\mathrm{SAC}}(t) = V_0 \cdot (1 - \exp(-\alpha_0 \cdot \vec{m}_E(t))),$$

$$\text{where } \vec{m}_E(t) = \vec{S}_{\mathrm{AVG}}(t) - \int_0^t \vec{v}_{\mathrm{SAC}}(\tau) \cdot d\tau. \tag{1.2}$$

The integration in Eq. (1.2) yields the current eye displacement signal, and implements a so-called resettable integrator (RSI; [22]); its value is reset to zero when the saccade has finished (and the eye foveates the goal specified by the SC). Although in some models this reset is proposed to have a relatively long time constant of about 50 ms, leading to large saccade errors at very brief (< 30 ms) intersaccadic intervals [26], we here take the reset as instantaneous [13].

In Eq. (1.2) we omitted, for ease of description, the decomposition of the vectorial saccade command into its respective horizontal/vertical movement components. In the vector averaging scheme this is implemented by a complex cross-coupling scheme for the horizontal and vertical burst generators (schematically indicated in Fig. 3(a) by H, V). This cross-coupling lowers the burst gains, $\alpha_{0,H} \cdot V_{0,H}$ and $\alpha_{0,V} \cdot V_{0,V}$, to account for component stretching and straight saccades (see above; [17, 27, 45]). To account for skewness of the saccade-velocity profiles (Fig. 1(b)), the static saturating characteristic of Eq. (1.2) should be dynamic too, e.g., by making the angular constant, α_0, time dependent. In this way, the slope of the characteristic toward saccade offset will systematically vary with the saccade amplitude.

To summarize, the averaging model of saccade generation (Fig. 3(a)) contains at least four nonlinearities: (i) vector averaging of the superior colliculus population activity; (ii) saturation of the brainstem burst generator to account for the nonlinear main sequence; (iii) fatigue of brainstem burst cells to yield appropriately skewed velocity profiles; (iv) cross-coupling between horizontal and vertical burst generators to explain straight oblique saccades and component stretching.

1.2.2. *Vector summation*

We recently proposed an alternative encoding scheme with only linear operations that accounts for the main sequence kinematics, and straight oblique saccades ([15], Fig. 3(b)). In this linear model, the SC motor map directly encodes the desired saccade trajectory through dynamic *linear vector summation* of its cell contributions:

$$\vec{S}_{\mathrm{LIN}}(t) = \sum_{n=1}^{N_A} \sum_{k=1}^{N_S} \vec{s}_n \cdot \delta(t + 20 - \tau_{k,n}), \tag{1.3}$$

with N_S the number of spikes of SC cell n (counted from 20 ms before saccade onset to 20 ms before saccade offset; the 20 ms being the SC-lead time); $\delta(x)$ is the Dirac impulse function (i.e., a spike); $\tau_{k,n}$ is the time of the k-th counted spike of cell n; $\vec{s}_n = \eta \cdot \vec{R}_n$ is the so-called "spike-vector" of cell n, which is the (tiny) eye-displacement vector generated by a single spike of cell n, where η ($\sim$ 1e-04) is a fixed scaling constant, which is identical for all cells [15, 48].

In this scheme (Fig. 3(b)), the burst generator is driven within a linear feedback circuit by motor error, which is specified by the integrated difference between the

instantaneous SC output, and the burst generator's velocity output (reminiscent to Scudder's model, [36])

$$\vec{v}_{\mathrm{SAC}}(t) = G \cdot \vec{m}_E(t),$$
$$\text{with } \vec{m}_E(t) = \int_0^t \left[\left(\sum_{n=1}^{N_A} f_n(\tau) \cdot \vec{s}_n \right) - \vec{v}_{\mathrm{SAC}}(\tau) \right] \cdot d\tau. \tag{1.4}$$

G is the (fixed) gain of the burst generator (i.e., no cross-coupling), and $f_n(t)$ is the instantaneous firing rate of cell n in the SC motor map (note that integration of the SC-firing rate over time is the same as computing the cumulative number of spikes, as in Eq. (1.3)). For simplicity, we here left out a small delay in the local feedback loop. Note that, according to this simple model, the instantaneous collicular output specifies the instantaneous eye velocity vector by:

$$\vec{v}_{\mathrm{SAC}}(t) = \frac{G}{1+G} \cdot \sum_{n=1}^{NA} f_n(t) \cdot \vec{s}_n. \tag{1.5}$$

Simulations that used measured spike trains from about 150 recorded neurons demonstrated that this simple model (only two free parameters: gain G and feedback delay τ) generated saccades with the correct trajectories, velocity profiles, and main-sequence behavior [15]. Further, the model makes two quantitative predictions for SC spike trains that were experimentally verified for the entire population of recorded cells: (i) the cumulative number of spikes of each recruited neuron and the instantaneous straight-line displacement of the eye between start and end position are linearly related, and (ii) the cumulative number of spikes, $N(t)$, is predicted by a precisely defined, dynamic extension of the classical movement field of Ottes *et al.* [29] (see [15], for details)

$$N(t) = \frac{N(R,\Phi)}{R} \cdot \Delta\hat{e}(t-20), \tag{1.6}$$

with $N(R,\Phi)$ the movement-field description for the total number of spikes in the burst ([29]; see the insets of Figs. 2(a) and 2(b) for an example), $[R,\Phi]$ saccade amplitude and direction, and $\Delta\hat{e}(t)$ the instantaneous, straight eye-displacement between the on- and offset positions (delayed by 20 ms).

1.2.3. *Main sequence*

Because the brainstem circuitry in the vector summation model is described by a linear feedback system, the nonlinear behavior of the saccade kinematics, the shape of the velocity profiles, and component stretching, should all be embedded in the spatio-temporal activity patterns of the SC motor map. The model and data described so far (and in [15]) do not specify how the population activity could encode these kinematic properties.

To study this point, we therefore first resorted to simulations with a computer model of the SC-brainstem system, in which we investigated the effect of different

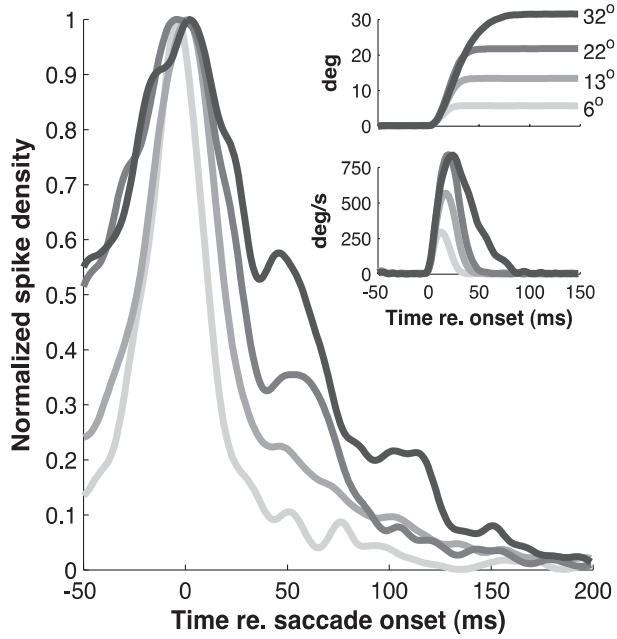


Fig. 4. Normalized burst profiles for SC cells at four different rostral-caudal locations have different skewness and burst durations. The number of spikes in these bursts, however, is highly similar. Small (6 deg) saccades have symmetrical bursts, those of large (32 deg) saccades are highly skewed. Insets show the associated average saccade position (top) and velocity (bottom) traces (adapted from [48]).

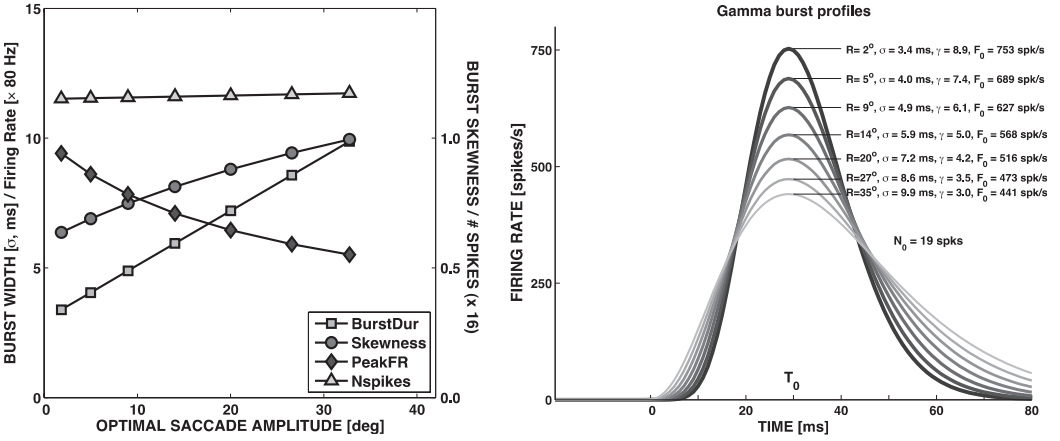
potential activity patterns [48]. These simulations used the well-established idea that static SC movement fields (quantified by the total number of spikes in the burst for a given saccade) are described by a spatial Gaussian activity profile in the SC motor map, with a width, $\sigma_{\text{pop}} \approx 0.5\,\text{mm}$, that is invariant across the SC [29]. Hence, with the assumption that the SC cell density is constant too, any given saccade recruits the same number of cells in the motor map.

We approximated the *temporal* profile of saccade-related bursts of each recruited cell in the population (illustrated in Fig. 4) by an asymmetric gamma-function:

$$f_n(t) = \kappa \cdot t^{\gamma} \cdot \exp\left(-\frac{t}{\beta}\right), \tag{1.7}$$

in which γ (dimensionless) is a measure for the burst skewness, and β (in ms) a parameter that sets the burst duration (Fig. 5(b)). The peak of the burst is determined by κ, and depends on the distance of the cell from the population center (in other words, on the distance between the cell's optimal saccade vector, $[R_n, \Phi_n]$ and the actual saccade for which it is recruited; see e.g. Fig. 2). The cell's peak firing rate is therefore determined by $F_{\text{pk}} \cdot \kappa$, with F_{pk} the peak firing rate at the center of the population. Note that in this formulation, all cells in the population have synchronized bursts.

So how does such a population generate the main-sequence kinematics? The simulations with the vector summation model showed that if the burst parameters $[F_{\text{pk}}, \gamma, \beta]$ are taken constant across the motor map (i.e., the same for all cells), the



(a) (b)

Fig. 5. Simulated burst properties of saccade-related cells in the SC motor map. (a) For all cells, the total number of spikes for their optimal saccade (Nspikes) is fixed; burst duration (BurstDur) and burst skewness both increase with the optimal saccade amplitude; peak firing rate (PeakFR) drops with amplitude, as $F_{pk} \propto 1/\sqrt{R_{\text{opt}}}$. (b) Burst profiles for locations at the rostral-to-caudal extent of the motor map (Eq. (1.7)). Compare with Fig. 4 (adapted from [48]).

total system behaves as a *linear* system: saccades will have fixed durations and linearly increasing peak velocities (like in Fig. 1(a), "L"). The only way to obtain the main sequence was by assuming that the burst profiles of Eq. (1.6) are not invariant across the map. The nonlinear main sequence of saccades (Fig. 1(a)) emerges when the firing rates of SC cells vary in a systematic way with their rostral-to-caudal location within the SC motor map: cells at the rostral zone (r in Fig. 3), encoding small saccades (i.e., they generate small spike vectors) have high peak firing rates (up to 700−800 Hz), short burst durations, and near-symmetrical burst profiles (large γ; see Fig. 4 for experimental evidence for this assumption). In contrast, at the caudal end (c) of the map, where large saccades are encoded (Fig. 3), peak firing rates are lower (down to 300−400 Hz), burst durations are longer, and burst profiles are positively skewed (low γ, [16, 48]; Fig. 5(b)).

In line with the recordings (Fig. 4), the total number of spikes in the burst was taken fixed across the motor map (at about 20 spikes for the central cell of the population), despite differences in the burst shapes ([15, 48]; Figs. 4 and 5), and strongly varying kinematics during blink-perturbed responses [14, 15]. Finally, the horizontal and vertical components of an oblique saccade in direction Φ are determined by linear vector decomposition of the radial velocity command (Eq. (1.5)), by scaling through synaptic weightings representing $\cos(\Phi)$ and $\sin(\Phi)$, respectively (i.e., no cross-coupling needed).

1.2.4. *Why vector averaging?*

The vector averaging scheme of the SC was first proposed by [23] to explain the pattern of changes of saccade endpoints after inducing a local, reversible

inactivation in the SC motor map. Interestingly, this subtle lesion affected the saccade metrics (i.e., their amplitude and direction) in a way that could not be predicted by linear vector summation, but was nicely in line with vector averaging. All saccade endpoints appeared to be directed away from the lesion: only saccades into the center of the inactivated spot were accurate; saccades to a site caudal (or rostral) from the lesioned site were hypermetric (or hypometric). Similar effects were seen for saccades with different directions. However, the inactivation also affected the saccade kinematics, as all post-inactivation saccades were slower (by about 20%) than control saccades of the same amplitude. The latter effect was not immediately predicted by vector averaging, as the averaging scheme (Eq. (1.1)) only specifies the saccade metrics. To account for the effect on kinematics, the authors assumed that somehow the SC firing rates influenced saccade velocity, presumably by affecting the gain (asymptote) of the brainstem burst generator [23, 27, 55] (Fig. 3(a)).

However, Goossens and Van Opstal [15] demonstrated that the same effects on saccade metrics and kinematics emerge from the linear vector summation model of Eqs. (1.3) and (1.5), provided one feature was added: the saccade would stop after reaching a fixed total spike-count criterion (i.e., it necessitates an active saccade-offset mechanism). In this way, when the center of the population is silenced by subtle chemical inactivation, the remaining active cells along the fringes of the Gaussian population, which have lower firing rates, will (i) produce a slower saccade, and (ii) will have to fire longer in order to reach the required total spike-count. Simulations of the summation model with real measured spike trains from about 150 SC neurons showed that the Lee *et al.* (1988) data on saccade metrics and kinematics could be reliably reproduced with this spike-count mechanism, which in fact introduces a brainstem nonlinearity. The recordings further supported the idea that recruited SC populations may indeed produce an invariant number of spikes for normal saccades across the oculomotor range [15].

1.3. *Target selection: Averaging and updating*

1.3.1. *Double stimulation*

When the visuomotor system is confronted with two visual stimuli presented simultaneously at different retinal locations, say at $\vec{T}_1$ and $\vec{T}_2$, it often programs an eye movement that lands at a location between the two stimuli [8, 28]. Since this response resembles the center-of-gravity of the retinal input vectors, its endpoint is usually described by a weighted vector-averaging response:

$$\vec{S}_{\mathrm{AVG}} = \frac{a \cdot \vec{T}_1 + b \cdot \vec{T}_2}{a + b}. \tag{1.8}$$

Here, a, b are fixed target weights that may depend on a number of different factors, like their relative saliencies and size [8], their spatial-temporal separation [2, 28], task constraints (e.g., target versus non-target), or on the saccade reaction time

[2, 28]. Because of the nonlinear scaling (division by $a + b$), Eq. (1.8) implies the existence of yet another nonlinearity in the visuomotor transformation underlying saccade programming.

Several studies have supported the idea that target averaging could be the underlying mechanism for dealing with multiple stimuli, and neurophysiological studies have suggested that such averaging occurs downstream from the SC motor map, in line with the assumptions of Eq. (1.1) (Fig. 3(a)). For example, electrical microstimulation at two locations within the SC motor map produces a saccade that resembles the weighted vector average of the two sites stimulated separately [31]. Recording studies have suggested that also under natural visual double-stimulation conditions each of the two visual stimuli induces an active population at the respective retinal sites in the motor map ([5], for express-latency saccades, and [30]).

It may be noted that the Edelman and Keller data [5] indicated that the peak activity at the two retinal target representations for express saccades was substantially lower than for the single-target control stimuli. This hints at the possibility that long-range inhibitory interactions ("winner-take-all") may govern the competition between different active populations within the SC motor map, a mechanism incorporated by [51] in a modification of the original ensemble-coding model [46] to explain Robinson's electrical double-stimulation results [31]. In this way, linear vector addition could in principle still account for presumed "downstream averaging", as in that case the summed output of each stimulated population (Eq. (1.3)) would be reduced by the lower firing rates.

Unfortunately, the exact spatial-temporal distribution of activity in the SC motor map under multiple-target conditions (knowledge that is crucial to apply the summation model; see below) is not well established. For example, other experiments had shown a single-peaked population in the SC motor map at the averaging site represents the averaging saccade in a double-stimulus saccade paradigm ([5], for regular-latency saccades; [11, 50]). These data therefore suggested that target averaging could have occurred *upstream* from the motor SC.

1.3.2. *Double-step paradigm*

When the two targets are presented in rapid temporal succession in a double-step, in which the first target rapidly changes direction (after a brief delay, Δt) toward a new location, strongly curved saccade responses may be observed [30, 47]. In the framework of Eq. (1.8), the double-step would involve a delayed activity at the retinal representation of target $T_2 : T_2(\Delta t)$.

The problem with the model of Eq. (1.8), also acknowledged by [30], is that it fails to account for experimentally observed curved trajectories in the double-step task. Such trajectories may start off in any initial direction, to eventually curve toward the final goal (see e.g., Fig. 6(b)). Not only does the averaging saccade of Eq. (1.8) have a wrong end-direction (note that its end-direction will be fully determined by the remaining activity at site T_2, and hence be parallel to the *retinal vector* T_2), it

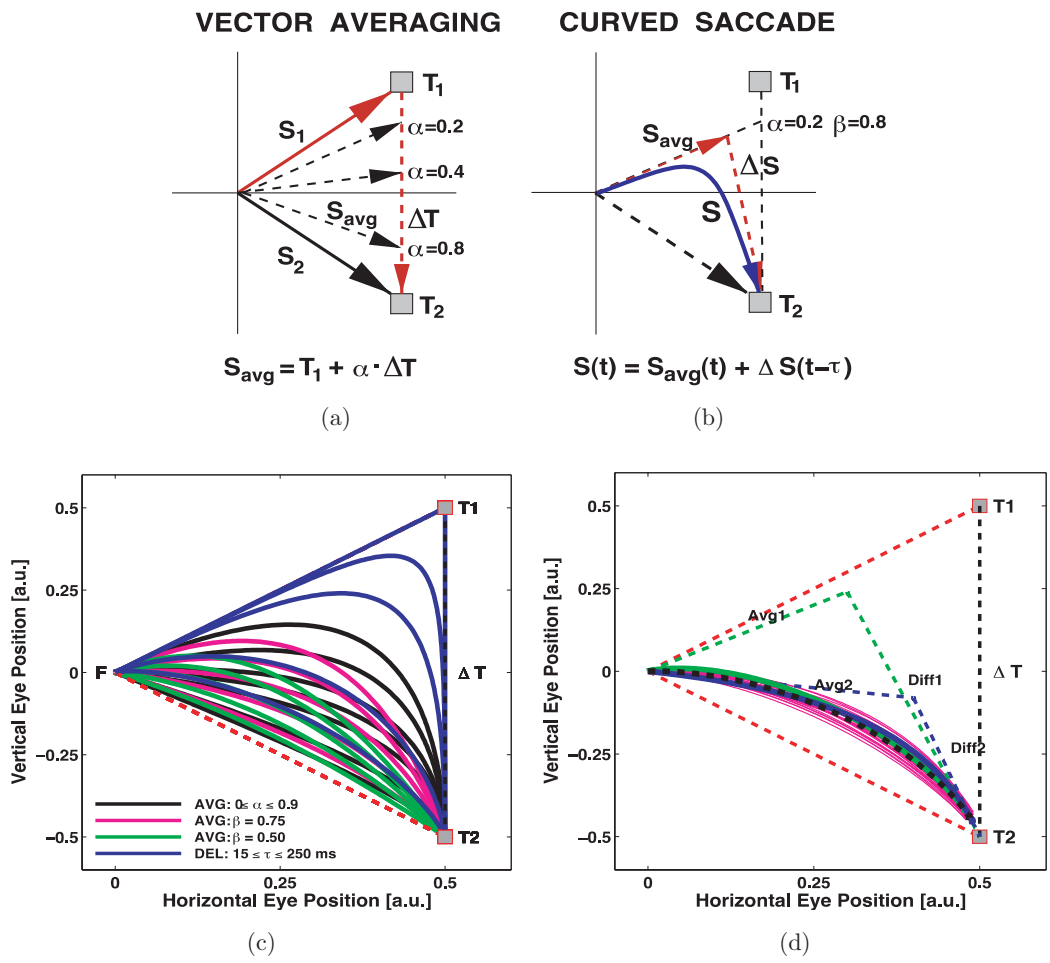


Fig. 6. (a) Linear vector computations could underlie saccade averaging (Eq. (2.1)), and (b) curved saccades (Eq. (2.2)). (c) An identical target configuration can thus give rise to a myriad of differently curved saccades and, similarly, (d) many different underlying motor commands for S_{AVG} and S_2 could result in very similar, curved trajectories (see text, for explanation).

also cannot reach the final end point at T_2 once the saccade has started off into a different initial direction.

A solution to this problem was incorporated in an improved version of the conceptual vector-averaging model by [55] (Fig. 3(a)) who simulated weighted vector-averaging saccades and curved trajectories. In the Walton model, the constant weights of Eq. (1.8) were replaced by time-varying weights at the two sites that represented the population activities:

$$\vec{S}_{\mathrm{AVG}}(t) = \frac{w_1(t) \cdot \vec{T}_1 + w_2(t) \cdot \vec{T}_2}{w_1(t) + w_2(t)}. \tag{1.9}$$

The vector-averaging model of Walton *et al.* ([55]; Eqs. (1.1) and (1.9)) assumes that the two retinal targets appear as consecutive active populations in the SC motor

map, and that the activity associated with the second target outlasts the first target. Accordingly, the "center-of-gravity goal" for the saccade will gradually shift during the movement from T_1 to T_2, and the saccade will curve in midflight to follow the dynamic goal, which eventually settles at the second retinocentric target location [55].

1.3.3. *Spatial updating*

So far, the described modeling efforts of target selection mechanisms did not incorporate the important concept of spatial updating within the visuomotor system. Robinson proposed that the saccadic system cannot rely exclusively on the retinal coordinates of a target to program its oculomotor response under dynamic conditions, and that it therefore employs feedback about its own oculomotor behavior (through efference copies of motor commands) to ensure spatial accuracy [32]. Behavioral double-step experiments showed that the saccadic system accounts for intervening eye movements to update the coordinates of briefly flashed visual stimuli in darkness [18], even when flashed in midflight of an ongoing head-unrestrained saccade [53].

In addition, electrophysiological studies had indicated that SC cells faithfully reflect the oculocentric target location (i.e., the oculomotor error), rather than the retinal locus of a flashed target, after an intervening saccadic eye movement. Interestingly, this was even the case when the saccade was not planned by the monkey, but evoked by the experimenter through SC micro-stimulation [38], but compensation for an electrically evoked eye movement did not occur when the stimulation was applied to the brainstem burst generator [39]. Those seminal experiments demonstrated that activity in the SC motor map corresponded to the true oculomotor error, required to direct gaze to the extinguished target location, and provided strong evidence that spatial updating for saccades employed an efferent feedback signal that occurred at or upstream from the recorded cells. Subsequent recordings in the frontal eye fields suggested that the visuomotor system keeps visual targets in an eye-centered reference frame by accounting for changes in eye position induced by intervening saccades [12].

An elegant series of neurophysiological experiments in posterior parietal cortex [4], frontal eye fields [42], and in midbrain SC [54], have later demonstrated that responses of many cells even *predict* the visual consequences of an upcoming, *planned* saccade. Hence, when the monkey programs a saccade, a cell in either of these areas signals an updated visual response *before* that saccade is even initiated, a phenomenon that was termed *predictive remapping*.

Here we speculate that predictive remapping, as well as stimulation-evoked updating (necessarily occurring during or after the evoked saccade), may use the same remapping mechanisms.

In this paper, we explore how spatial updating might be incorporated in the framework of the vector-summation model, by showing that target averaging and the programming of goal-directed curved saccades in the double step

paradigm may in fact be understood from linear vector operations, in combination with predictive remapping.

2. Methods and Results

2.1. *Oculocentric remapping revisited*

When the saccadic system responds with two saccadic eye movements to a double-step target jump, the respective oculomotor error signals are determined by the first retinal target location, T_1, and by the difference between the retinal stimuli, respectively:

$$\vec{T}_1 \quad \text{and} \quad \Delta\vec{T} = \vec{T}_2 - \vec{T}_1. \tag{2.1}$$

Since predictive remapping holds that the second signal is already available to the system before the first saccade is executed (see Introduction), we here note that the "averaging" response of Eq. (1.8) could then also be formulated as the linear vector sum of these two signals:

$$\vec{S}_{\text{AVG}} = \vec{T}_1 + \alpha \cdot \Delta\vec{T} \quad \text{in which } 0 \leq \alpha \leq 1. \tag{2.2}$$

When $\alpha = 0$ the first saccade is directed toward T_1, for $\alpha = 1$ it is directed toward T_2, whereas for $\alpha = 0.5$ it goes towards the midpoint (Fig. 6(a)). Thus, the coordinates of the averaging saccade could simply be determined by weighted linear vector addition, without the need for a nonlinear scaling mechanism.

Conceptually, parameter α could correspond to the relative activity level of the population associated with the developing difference vector. It could vary from trial to trial, and may e.g., depend on visual stimulus properties (stimulus timing, intensity, size), or on the latency of the first saccade. However, regardless of the mechanism that modulates α, the point is that experiments have shown that the coordinates of the difference vector are already available before the start of the first saccade.

A complete linear parameterization of curved saccades can also account for the possibility that the first response is not directed toward T_1, but is an averaging response that may only be partially executed (amplitude gain β, with $0 < \beta < 1$). Behavioral experiments have shown that the saccadic system indeed accounts for the trial-to-trial variability in its own motor performance [13, 53], so that the programming of the second saccade vector incorporates the coordinates of the actual first saccade, S_{AVG}, rather than the retinal target coordinates of T_1 and T_2.

In our extended vector-summation model, a curved saccade is thus determined by the linear sum of two overlapping motor commands, in which the second, delayed, command accounts for the metrics of the first response:

$$\begin{aligned} &\vec{S}_{\text{SUM}}(t) = \vec{S}_{\text{AVG}}(t) + \vec{S}_2(t-\tau), \quad \text{with } \vec{S}_2(t) = \vec{T}_2 - \vec{S}_{\text{AVG}}(t) \quad \text{and} \\ &\vec{S}_{\text{AVG}} = \beta \cdot (\vec{T}_1 + \alpha \cdot \Delta\vec{T}). \end{aligned} \tag{2.3}$$

Equation (2.3) contains three free parameters, which give rise to a myriad of curved responses for an identical target configuration: α (the amount of "averaging", Eq. (2.2)), β (the gain of the averaging saccade), and delay τ. Note that if $\beta = 1$, the second saccade is simply determined by $\vec{S}_2 = (1 - \alpha) \cdot \Delta\vec{T}$.

Figures 6(c) and 6(d) show a number of examples that were simulated according to Eq. (2.3), using simplified Gaussian velocity profiles. In Fig. 6(c) we generated trajectories for a variety of parameters (black traces: $0 \leq \alpha \leq 0.9$, $\beta = 1$, and $\tau = 70$ ms, showing various amounts of averaging; magenta and green traces: $0 \leq \alpha \leq 0.9$, $\tau = 70$ ms, and $\beta = 0.75$, versus 0.50; blue traces: $\alpha = 1$, $\beta = 1$ and $\tau = 15$, 30, 100, 150 and 250 ms. In the last case, the first saccade briefly stopped at T_1, before continuing with the difference response).

Figure 6(d) illustrates the point that many different combinations of S_{AVG} and S_2 can give rise to highly similar trajectories. In this simulation, the black "target trace" served as a measured template ($\alpha = 0.4$, $\beta = 0.7$ and $\tau = 35$ ms) for which the underlying motor commands were subsequently estimated by a brute-force search across 8000 different $[\alpha, \beta, \tau]$ combinations. The magenta traces are solutions that differ by less than 2% from the target trajectory (considered to fall within the measurement resolution). The green and blue examples highlight two very different solutions for the two motor commands that yet yielded nearly identical trajectories.

This point therefore illustrates an important problem, namely that if vector summation were to be the mechanism underlying saccade updating, SC recordings at one or two sites will not suffice to unravel the two underlying motor commands, as they could vary tremendously from trial to trial, without affecting the emerging trajectories.

Figure 7 illustrates a full simulation of a curved saccade response by the vector-summation model, according to Eqs. (1.5) and (2.3). The MatLab implementation of this model is the same as described in [48].

In this simulation, the two targets at $[R, \Phi] = [20, \pm 45]$ deg induced a brief visual response in the visuomotor cells, followed by motor activity, which is relocated to two different sites within the SC, given by $\alpha = 0.4$, $\beta = 0.9$, and a delay $\tau = 30$ ms.

2.2. *Curvature in single-target responses*

In the vector-averaging model, the nonlinear horizontal and vertical burst generators are coupled through mutual inhibition to reduce the gains of the burst generators in a way that depends on amplitude and velocity of each response component. This additional nonlinearity is introduced so as to produce straight oblique saccades. Because the burst generators have linear characteristics in the vector-summation model, such a precisely tuned coupling is not required. In this model, the burst generators are independent, but saccades are straight because (i) the cells in the SC population fire roughly synchronously [15, 16], and (ii) the gains and delays in the local feedback loops are taken identical.

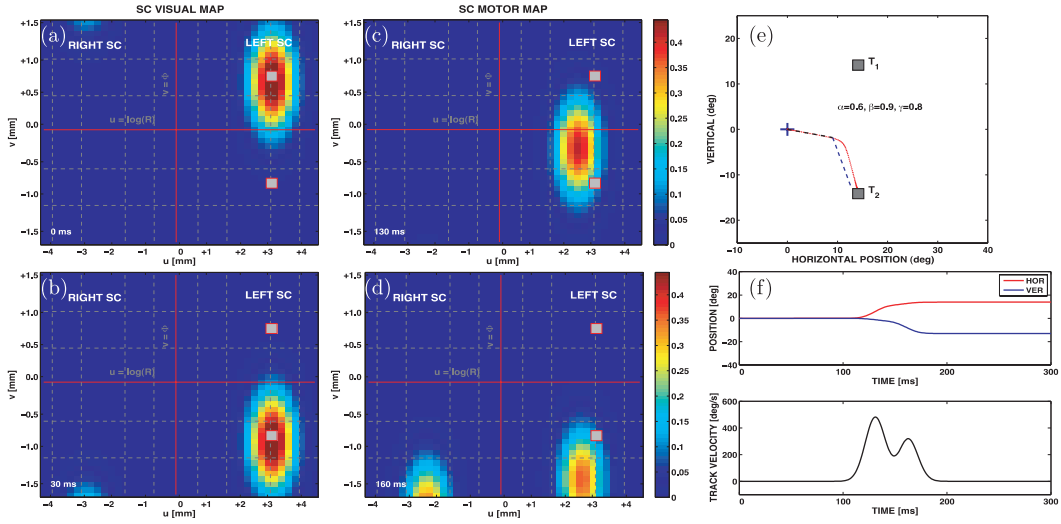


Fig. 7. Simulation of a curved saccadic response by the output of the motor SC. The curved saccade consists of an initial averaging saccade, temporally overlapping with a second saccade toward the final goal (with $\alpha = 0.6$, $\beta = 0.9$, and delay, $\tau = 30$ ms). The visual activity of the SC cells (a–b) arises at the retinal representations of the target locations, at two different moments in time, 30 ms apart. The motor map (c–d) shows the initial motor response at $t = 130$ ms toward the averaged location (c), followed by motor activity at the right-downward representation, here shown at $t = 160$ ms (d). In (e), the resulting saccade trajectory (red trace) is shown; the blue dashed lines correspond to the two underlying individual saccade vectors S_{AVG} and S_2, respectively. Panel (f) shows the horizontal/vertical eye positions and corresponding radial eye velocity as a function of time.

Notwithstanding, this model also can readily produce curved saccades toward single targets. For example, when the BG gains differ, both burst generators produce different component kinematics, and saccade trajectories curve toward the faster component. A simulation of Niemann-Pick Type C disease [33] with the linear summation model provides an extreme example of this uncoupled component kinematics (Fig. 8). In this simulation, the gains of the burst generator feedback loops were set to $B_H = 80$ and $B_V = 8$, respectively.

Note that another mechanism by which the SC population could in principle produce a curved saccade would be by desynchronizing activity among the cells within the neural population. However, our recordings indicated that for saccades evoked by a single target this simply does not happen, as the saccade-related bursts within the active population appear to be highly synchronized [16].

In summary, according to the vector-summation model, nonlinearities in the spatial processing within the saccadic system ("*target averaging*", and "*curved double-step responses*") could result from linear vector processing through oculocentric spatial updating (*predictive remapping*), whereas the nonlinear saccade kinematics ("*main sequence*", "*skewness*", "*component stretching*") could all result from a *rostral-to-caudal shaping* of the SC burst profiles, followed by dynamic linear addition of all cell contributions at the brainstem burst generators.

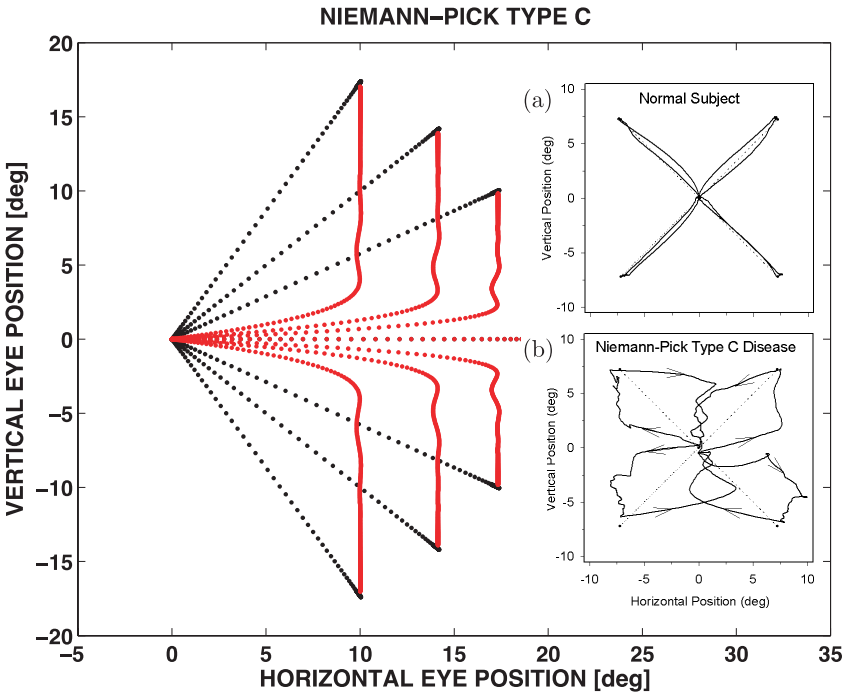


Fig. 8. Simulation of Niemann Pick Type C disease, for which failure of the vertical burst generator is assumed. This was simulated by setting the gains of the burst generators for horizontal and vertical saccade components to $G_H = 80$ and $G_V = 8$, respectively. Feedback delays are 4 ms. Insets: (b) patient data, and (a) normal oblique saccades (from [33], with permission).

3. Discussion

3.1. *The SC as optimal controller*

This paper compares two conceptual models that propose how the midbrain SC is involved in the generation of a saccadic eye movement: the vector-averaging model versus the vector summation model. Both models can account equally well for a myriad of well-known saccade behaviors: the nonlinear kinematics of the main sequence, the skewness of saccade velocity profiles, component stretching in oblique saccades, and target averaging. Note also that both models place the motor SC outside the local feedback loop of saccade generation: both rely on the experimental finding that the population of recruited cells for a saccade stays at a fixed location in the motor map (i.e., no moving population). However, the models disagree about the role of the SC in specifying the saccade kinematics. In the vector summation model, the SC output represents a dynamic, desired eye-displacement signal (i.e., a feed-forward motor command signal), represented by the cumulative number of spikes in the bursts of all recruited cells; the vector-averaging scheme provides a gaze-motor error signal (the saccade goal) to the brainstem.

Although the mean level of SC activity has been proposed before to influence saccade kinematics, e.g., by affecting the characteristics of the brainstem burst

generator [27, 40, 55], the precise mechanism of this putative pathway has remained elusive, and at best, speculative. Similar problems haunt the neurocomputational implementation of the vector-averaging process: although mathematically straightforward (Eq. (1.1)), it remains unclear and highly nontrivial how downstream averaging of cell contributions is carried out by neurons at the midbrain-brainstem interface.

In contrast, despite its utmost simplicity (only two free parameters to predict the kinematics of all saccades), the observed saccade nonlinearities are emerging properties of the linear summation model, without additional assumptions. Moreover, the measured spike trains of saccade-related bursts in the SC follow the predictions of the spike-count model with high accuracy [15, 48].

Because the spike-summation model assumed (for the sake of argument) a *linear* brainstem circuitry, the observed nonlinearities in saccade behavior should be somehow embedded in the spatio-temporal activity patterns of the motor SC. A theoretical analysis, combined with experimental support, indicated that the main-sequence nonlinearity and velocity skewness are due to a spatial gradient across the rostral-to-caudal (i.e., amplitude) dimension of the motor map. Rostral cells fire high frequency, short, and symmetric bursts for their optimal saccade, whereas caudal cells produce lower firing rates, and longer-duration, skewed burst profiles. These properties strongly suggest that the main sequence of saccades is not due to a passive nonlinear characteristic in the brainstem (like neural fatigue, and saturation), but rather implement a *deliberate neural control strategy.*

Given the function of saccades (redirect the fovea as fast and as accurately as possible to the target), in combination with internal constraints (neural noise, poor spatial resolution in the peripheral retina), Harris and Wolpert demonstrated on the basis of a theoretical analysis that the main sequence is an optimal solution in the sense of speed-accuracy trade off [19]. As the analysis was applied to horizontal saccades only, it could not dissociate brainstem nonlinearities from collicular nonlinearities. However, when considering two- (or even three-) dimensional control of eye movements, or combined eye-head gaze shifts, the motor SC is ideally suited to implement such an optimal control strategy. With a single, vectorial nonlinear burst generator, implemented in the SC motor map, the main sequence is guaranteed for all saccade directions, for which straight oblique saccades are a mere byproduct, without the need for complex, dynamic cross-coupling of the horizontal and vertical nonlinear burst generators.

Note that in the vector summation model, the saturation of peak-eye velocity in the main sequence for large saccades results from two opposing factors: (i) lower firing rates at caudal sites, which roughly follows the inverse of the square-root of saccade amplitude (see [48]), versus (ii) the exponential increase of synaptic efficacy with the SC rostral-caudal coordinate ($w \propto \exp(u)$, with u running from 0 (fixation area) to about 4 mm) according to the efferent mapping function [29]. If peak-firing rates at rostral and caudal cells would be the same, peak eye velocity would increase linearly with saccade amplitude. Since we see no obvious physiological reason as to

why caudal cells would fire at lower rates than rostral cells, we conjecture that this gradient implements a deliberate, functionally relevant, design within the gaze-control system.

This putative role in optimal motor control is obviously not in line with the goal-hypothesis for the SC output population. Indeed, it is difficult to reconcile the tight correlations of instantaneous firing patterns of SC cells with the ongoing eye-movement kinematics (Eqs. (1.5) and (1.6)), and the rostral-caudal gradient of burst properties (Fig. 4), without accepting an explicit role for these cells in oculomotor control.

3.2. *Averaging mechanisms*

Several phenomena could resemble "vector averaging", that may nonetheless result from quite different mechanisms. The weighted vector-averaging operations of Eqs. (1.1), (1.8) and (1.9) produce the center-of-gravity of the contributing cells in motor (or visual) space. The same holds for the linear vector operation described by Eq. (2.2). Indeed, the two are equivalent in their predictions, although the underlying mathematics (nonlinear scaling, versus linear vector addition) is quite different.

However, there is a third way in which neural activity of the SC motor map could produce responses that may resemble a weighted average. For example, an intrinsic local excitatory−global inhibitory network between SC cells (e.g., a Mexican hat connectivity pattern) would lead to competition between distant neural populations, e.g., at the neural images of T_1 and T_2, that either produces a winner-takes-all activation at one of the sites, or to reduced activities at either site. Such a mechanism operates in collicular space, and although the result will strongly deviate from the linear addition of the vectors corresponding to T_1 and T_2, it is not a proper vector average either (e.g., [51]). This third mechanism could underlie the results observed for synchronous electrical double stimulation at different collicular sites [31], and may also explain the observed neural responses for saccades evoked at express latencies by visual double stimuli [5]. In the latter case, the visual responses at the original retinal locations are thought to merge with the short-latency motor activities, which then would interact through the Mexican hat connections. For longer reaction times, however, predictive remapping (Eq. (2.2)), or proper averaging at an upstream processing level (e.g., in frontal eye fields, or posterior parietal cortex), could relocate the neural activity in the SC motor map to the appropriate motor representation (as illustrated in Fig. 7).

3.3. *Comparison to the skeletal motor system*

Cells in the primary motor cortex (M1) of primates are tuned for arm-movement direction, and the "*population-vector*" hypothesis [9, 10] describes how the weighted contributions of M1 cells encode the arm-movement direction by:

$$\vec{P}_{\text{arm}} = \sum_{n=1}^{N_A} f_n \cdot \cos(\phi_n) \cdot \hat{e}_n, \tag{3.1}$$

with f_n a neuron's firing rate, and φ_n, the arm-movement angle re. its preferred unity direction vector, $\hat{e}_n$.

Note that the spatial tuning of M1 cells differs fundamentally from the movement-field tuning of SC cells: first, the directional tuning of SC cells is restricted to about 60 deg, and is therefore much narrower than the cosine tuning of M1 cells (see e.g., Fig. 2(b)); second, unlike SC cells, responses in M1 do not appear to be restricted for movement amplitude. In that respect, the spatial tuning of M1 cells is reminiscent to the movement fields of brainstem burst cells in PPRF and riMLF, which are also cosine tuned (Fig. 3). A theoretical analysis demonstrated that a uniform population of independent cosine-tuned cells always provides an accurate estimate of the effector's movement direction, and that therefore the population vector concept just reformulates that neurophysiological fact [34]. However, Scott *et al.* demonstrated that the distribution of optimal movement directions, $\hat{e}_n$, of M1 cells was not uniform, and that the reconstructed population-vector thus systematically deviated from the actual direction of hand movements in the horizontal plane [35]. In other words, M1 activity appeared not to encode movement within a hand-based reference frame. Instead, a better model to explain the tuning characteristics of M1 cells accounted for mechanical anisotropies of the shoulder joint (quantified by joint power) for different movement directions.

In line with the conclusions of [35] for monkey M1, local activation and stimulation studies performed in cat motor cortex also suggested a strong relationship between evoked M1 activity and selective muscle synergies [3]. For example, iontophoretically administered bicuculline (a $GABA_A$ antagonist) in the cat's forelimb area led to a limited, but extended, spread of neural excitation of about $7\,mm^2$ around the injection site. The estimated size of the activated population (standard deviation about 0.7 mm) is similar to that reported for electrical microstimulation in the midbrain SC [15, 25, 29] (s.d. 0.5−0.7 mm), although the spatial neuro-anatomical connectivity in both structures is much more extensive. The limited neural excitation may be understood from the normalizing effects of a local excitatory−global inhibitory reciprocal network (see also above), effectively tuning the neural population [3, 51].

Interestingly, when applying simultaneous electrical double stimulation at different sites within the cat's motor cortex, Ethier *et al.* reported excellent correspondence with the prediction of linear vector summation for the directions of the individual stimulation effects on evoked forelimb movements [6]. Yet, the magnitude of the double-stimulation movement was typically smaller than predicted by linear vector summation. These results are qualitatively in line with similar "averaging" effects of saccadic eye movements, observed for double stimulation in the monkey SC [31]. As explained above, such averaging is probably caused by neural interactions within the intrinsic neural network between the two activated sites, rather than by a vector averaging mechanism operating in motor space. Without the assumption of Mexican hat-like connectivity within the SC, the summation model of Eq. (1.3) produces linear vector summation of the effects of

individual sites. However, as the saccade is terminated whenever the total spike count reaches the preset, fixed, population threshold, the motor output will still be restricted to the approximate "vector average" when both sites are stimulated above threshold, as in that case:

$$\vec{S}_{\mathrm{SUM}} = p \cdot \vec{S}_1 + q \cdot \vec{S}_2, \tag{3.2}$$

where p and q are the relative stimulation strengths, and the constraint $p + q = 1$ sets the spike-count cut-off (compare with Eqs. (2.1) and (2.2)). Nonetheless, linearity will be preserved at low stimulation strengths, when either site produces a saccade that is much smaller than the optimal vector for that site ($p + q < 1$) [51, 52]. Under those conditions, the linear vector sum still remains below the cut-off threshold for saccade termination. Whether such effects indeed occur for double stimulation within the SC motor map and the primary motor cortex remains to be tested.

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THE MOTOR FUNCTIONS OF THE BASAL GANGLIA

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The past 25 years have seen a resurgence of interest in the basal ganglia. In the 1980s, a series of studies yielded the now classic descriptions of basal ganglia connectivity and information flow that now dominates textbook descriptions. This was followed by the appearance of reward-based learning theories of corticostriatal function in which dopamine played a critical role in modulating corticostriatal connectivity. These advances have contributed enormously to our understanding of the basic principles of some of the circuits within these structures, and have dominated novel approaches to treatment of basal ganglia diseases. Yet even so, many of the common symptoms of Parkinson's disease or dystonia are incompletely understood, suggesting that these "dark basements of the brain" still harbor hidden secrets.

Keywords: Basal ganglia; movement; dopamine; Parkinson's disease; deep brain stimulation.

1. Introduction

Although the basal ganglia has a role in cognitive and emotional processing, much of our knowledge, particularly about the pathophysiology of these nuclei, has arisen from studies involving the motor system. From one point of view, these approaches have been highly positive and have led to a resurgence of interest in novel treatments for common diseases of the basal ganglia such as Parkinson's disease and dystonia. However, from the point of view of a clinician trying to understand the symptoms of the commonest disease of the basal ganglia, Parkinson's disease, the detailed pathophysiology often seems woefully inadequate: it may have some implications for bradykinesia but is incapable of explaining the other common symptoms of tremor, rigidity and postural instability.

2. Anatomy

The basal ganglia comprise a group of subcortical nuclei comprising the striatum, globus pallidus, subthalamic nucleus (STN), and substantia nigra. The main connections between them and the pattern of information flow between them are summarized in Fig. 1. Note that the striatum in rodents is a single structure whereas

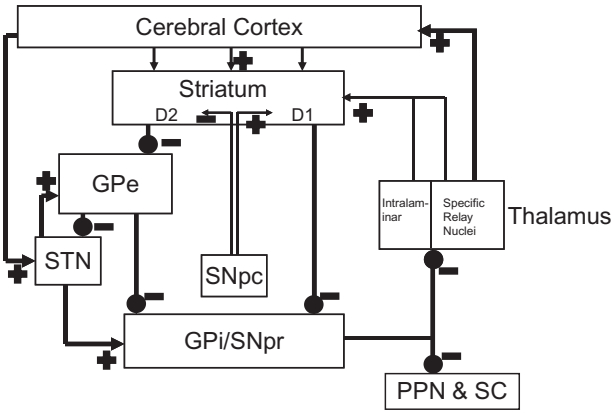

Fig. 1. Summary diagram of the major connections in the basal ganglia. Excitatory connections are shown as black arrowheads with "+"; inhibitory connections are indicated as black circles with "–". GPe, external segment of globus pallidus; GPi, internal segment of globus pallidus; SNpr, substantia nigra pars reticulata; SNpc, substantia nigra pars compacta; STN, subthalamic nucleus; PPC, pedunculopontine nucleus; SC, superior colliculus. D1 and D2 refer to postsynaptic receptor subtypes of the neurotransmitter dopamine.

it consists of two separate structures, the caudate and putamen in primates. Conversely, the globus pallidus and substantia nigra are each viewed as consisting of two separate structures. The internal and external segments of the globus pallidus (GPi and GPe) share some but not all of their input and output connections. The substantia nigra pars reticulata (SNpr) has similar connections to the GPi, whereas the pars compacta (SNpc) consists of a quite different population of dopaminergic cells whose axons innervate the striatum. The inputs to the SNpc are not shown on the diagram since the importance of the various known anatomical inputs is not known. However, connections from striatum (particularly caudate nucleus) and habenula may well be important.

2.1. *Main connections and information flow*

Despite its close involvement in movement control, the basal ganglia have no direct sensory inputs or motor outputs. The main information flow seems to be in a loop from cortex to basal ganglia and back to cortex [1]. Figure 1 shows the striatum can be regarded as the main receiving nucleus for cortical inputs whereas the GPi/SNpr represents the main output channel, via thalamus, back to cortex. Input from the cortex is excitatory and glutamatergic whereas the output is GABAergic and inhibitory. Within the basal ganglia, the striatum is connected to the GPi/SNpr via two separate sets of connections known as the direct and indirect pathways. The striatum inhibits the GPi/SNpr via the direct pathway whereas the overall effect of the indirect pathway is excitatory. Finally, note the additional cortical input to the STN: this is termed the "hyperdirect" pathway since it avoids the striatum [2, 3].

2.2. *Additional connections*

There are two other sets of connections to highlight in this diagram. First, although the majority of the output goes via thalamus back to cortex, there is some output to several brainstem nuclei including the superior colliculus (SC) and pedunculopontine nucleus (PPN). The former is related to the role of the basal ganglia in eye movement whereas the latter may have a role in gait and posture, and has recently been used as a target for deep brain stimulation in patients with Parkinson's disease who suffer from postural and gait problems [4]. The second connection to note is the input and output from the midline thalamic nuclei that mimics that from the cortex.

2.3. *Parallel organisation*

Although the cortex innervates the striatum topographically, with prefrontal cortex projecting onto the head of the caudate and sensorimotor cortex onto the putamen, the overlapping dendritic trees of receiving neurons in the nuclei of the basal ganglia would appear to be designed to integrate information from many cortical areas [5]. Despite this, physiological studies suggest that input from particular cortical areas remains separate on its way through the basal ganglia circuits. Most authors describe four or five main circuits [1]: this article focuses on the two of them, the oculomotor loop from frontal eye fields to caudate without output back mainly to the superior colliculus, and the sensorimotor loop from sensory and motor cortical areas to putamen and thence back to cortex or pedunculopontine nucleus. In normal conditions, the information is segregated even within these pathways. For example, motor inputs from premotor, supplementary motor and primary motor areas project to different subregions of the GPi. Sensory inputs from arm and leg also remain separate. However, in the absence of dopamine, segregation breaks down and somatotopy becomes much less clear.

2.4. *Striatal anatomy and dopaminergic input*

Ninety percent or more of the neurons in the striatum are medium spiny neurons; the remainder are mostly cholinergic and GABAergic interneurons [6]. The spiny neurons receive cortical (and thalamic) inputs onto the tips of the dendritic spines and have axons that project to the globus pallidus. One subpopulation of neurons send axons directly to GPi/SNpr whereas the other forms the origin of the indirect pathway and projects to GPe. In addition, there is a diffuse dopaminergic input from the SNpc that terminates at the base of the dendritic spines, in a strong position to modulate the action of the cortical and thalamic inputs at the tips. Neurons of the direct pathway contain mainly D1-type dopamine receptors whereas those of the indirect pathway are mainly of the D2 variety.

GABA interneurons also receive input from cortex and densely innervate the cell bodies of spiny neurons. Their function is unknown but they could mediate a feedforward cortical inhibition of spiny neurons that might terminate initial

excitation. Cholinergic interneurons are large and are active in the absence of inputs ("tonically active neurons", TANs). They have widespread terminals and cholinergic receptors are found on spiny neurons and at dopaminergic and glutamatergic synapses.

3. Physiology of Sensorimotor Basal Ganglia

The first ideas about the role of the basal ganglia in motor control were driven by the observation that at rest, the output neurons of the GPi/SNpr fire at sustained high rates of 60 Hz or more [7]. Given that they are GABAergic, this was thought to provide tonic inhibition of the thalamus and thus withdraw facilitation from motor cortex. If inhibition was removed, facilitation would be restored and movements could occur. Observations of activity in the oculomotor loop during visually triggered saccadic eye movements were consistent with this. During fixation, activity in the part of the SNpr that projects to superior colliculus was high, but was suppressed shortly after a visual stimulus was presented in the periphery. This was followed by a burst of activity in the superior colliculus and movement of the eyes. Shortly afterwards, SNpr activity rose to baseline levels. It appeared as if appearance of the visual stimulus had released the brake of the basal ganglia and allowed the eyes to move.

However, a further experiment showed that this link was not obligatory [8]: depression of SNpr activity did not necessarily cause movement of the eyes. In this experiment, monkeys were trained to make a memory guided saccade. They fixated a central spot; a target was presented briefly to the right or left, but the monkey had to retain fixation until the central spot disappeared, at which time it had to make a saccade to the remembered position of the target. Discharge rates in SNpr declined on presentation of the target and stayed depressed until the fixation spot was extinguished and the eyes had moved to the remembered target. In this case, it was as if the depression of SNpr activity served as a form of memory of the target location. However, eye movement itself was delayed and presumably initiated by some other mechanism.

A series of later experiments in a number of different laboratories attempted to extend such observations to the control of upper limb movements. However, the results were unclear. Arm movement-related cells were found in striatum and pallidum, but their relationship to movement parameters was complex and confusing [9]. In retrospect, this may have been because the tasks studied were similar to those designed to explore primary and secondary motor areas of cortex, where there is a much closer relationship of cell discharge to movement. In the basal ganglia in contrast, there was no clear relationship of cell discharge to movement speed, extent, direction or whether the movement was slow and smooth or quick and ballistic. In fact, the discharges could appear linked to movement extent in one task but not in another. In most cases, cells changed their discharge rate after movement onset, suggesting basal ganglia was not important in the initiation of movement,

which seemed surprising in view of the difficulty that patients with Parkinson's disease have in starting to move. Finally, lesioning the output nuclei with kainic acid produced little change in movement, except to slow it a little and increase the amount of co-contraction around wrist or elbow joints [10].

The results suggested that the basal ganglia output was not essential for movement, at least in the adult animals in which it was tested. Instead, it seemed to be necessary to facilitate movement, perhaps reducing the computational overhead of cortical areas to which it projected. Mink's model of basal ganglia output incorporates this idea within a center-surround framework [11]. He proposed that the basal ganglia output was focused spatially, and perhaps temporally such that it would facilitate (by withdrawing ongoing inhibition) some movements and suppress others. It did not trigger movement onset but refined cortical output patterns. This explained why neurons sometimes seemed to discharge completely differently in apparently very similar tasks. It also accounted for the increase in co-contraction that had been observed when GPi output was interrupted either by kainate injection or by electrical stimulation [10].

In the initial formulation of Mink's model, the STN played an important role in providing a background tonic facilitation of the GPi/SNpr, and hence a generalized inhibitory output to motor structures. The direct pathway from striatum was viewed as providing a focused input that suppressed GPi/SNpr neurons in highly specific spatial patterns. This inhibitory input led to focal reductions in the inhibitory output of the basal ganglia which were ultimately responsible for focusing activity in motor cortex. The global role of the STN input resulted from a belief that STN projections were distributed widely to the dendrites of GPi/SNpr neurons whereas the direct input from striatum was much less divergent and could thus issue a focused motor command. However, this dichotomy may not be correct, and it seems likely that patterned activity in both direct and indirect projections would be needed to produce a focused output as envisaged by Mink.

In summary, the basal ganglia are seen as providing a general inhibitory output to movement. The circuitry within these structures is thought to release inhibition in a highly selective way, both in space and time so that in any given context, appropriate movements are facilitated whereas others are suppressed. Importantly, the outputs are not believed to trigger movements but only to bias the motor system towards certain patterns of movement that are likely to be encountered as the animal moves in its environment. The next question becomes how the patterns of output are selected from the many inputs that the basal ganglia receive. This is the realm of dopamine and reinforcement learning.

3.1. *The role of dopamine*

In the model of Mink, the patterned output from GPi/SNpr is the result of a patterned input from striatum. But how this pattern is set up? A series of experiments by Schultz and others on the role of dopamine provides a possible explanation [12].

Dopaminergic projection neurons in the SNpc normally fire at a slow rate of around 5 Hz, but occasionally produce short bursts of higher frequency activity. Schultz found that the bursts occurred when animals received an unexpected reward.

The dopamine neurons have highly divergent terminations in the striatum with each axon forming connections with many hundred striatal neurons. Thus, a burst of dopaminergic firing will lead to very widespread dopamine release in the striatum. As noted above, this input, at the base of the dendritic spines of the medium spiny neurons is in a position where it could modulate the input which arrives from the cortex at the tips of the spines. It has been postulated that a correctly timed dopamine input could change the efficiency of cortical inputs, such that unexpected rewards would reinforce immediately preceding inputs that might have led to the reward. Effectively, this is the basic premise of all striatal models of learning. It allows the striatum to learn patterns of outputs that in any given context bias movement selection towards actions that lead to reward. The striatum is seen as an essential learning machine that automatically decides (on the basis of prior experience) which movement is likely to lead to the best outcomes.

Each striatal medium spiny neuron receives input from several thousand different cortical neurons on its spines. The input from each synapse is weak and many inputs are needed to discharge the neuron. This convergent input from cortex is complemented by the divergent dopaminergic signal from SNpc. Striatal learning models suggest that patterns of input that discharge the neuron and lead to a subsequent unexpected reward will be reinforced by the dopamine burst. Thus, the striatum can be "taught" to recognize patterns of input and on receiving one of these will produce the appropriate output that is most likely to lead to reward. The cortex is therefore using the striatum to select appropriate patterns of output which reinforce behaviors which are likely to lead to reward.

It is important to note that the dopamine burst occurs with unexpected rewards but not with expected reward; indeed, if an expected reward is absent or worse than expected, the dopaminergic activity is reduced. This means that synaptic connections do not get saturated, and that the system is always seeking out the best possible pattern of behavior. The dopamine signal is therefore said to signal reward prediction error. Formal models of this sort of behavior describe what is called "actor-critic" learning. The "actor" is the striatum which is instructed by the "critic" (dopamine) when its performance could be better than it is at present and it is punished (lack of dopamine) when it performance is worse than expected [13].

There is some evidence that the D1 and D2 receptors on the direct and indirect projection neurons may play different roles in this learning scheme [14]. D1 receptors have a lower affinity for dopamine than the D2 receptors, which are thought to be more fully occupied even at basal tonic levels of dopamine firing. Thus, D1 receptors are more likely to be able to respond to bursts of activity and reinforce connectivity in the direct pathway. This would remove inhibition from outputs that lead to reward. Conversely, the D2 system might be more sensitive to withdrawal of dopamine in unrewarded trials. It has therefore been suggested that the D2 system

might operate in the opposite way to the D1 system, reinforcing inputs that are active in the absence of reward. This would mean that activity patterns in the indirect pathway, which maintain strong inhibitory output from the GPi/SNpr are reinforced by lack of reward. In simple terms, punishment (viewed as lack of reward) would be associated with patterns of activity that reduce the probability of performing the punished action.

Although dopamine neurons fire primarily in response to unexpected rewards, they can also in many standard experimental paradigms be shown to shift their firing in time such that rather than firing after presentation of reward they fire after presentation of a signal that predicts the upcoming presence of reward [12]. For example, in a remembered saccade task, a target might appear briefly on the right or left of fixation; after an interval, the fixation light might be extinguished to signal that the animal should move the eyes to the remembered target. If movements to the right are rewarded, then initially, dopaminergic neurons might fire on receipt of the reward. However, after many trials, they may shift discharge to the time of the target presentation, increasing activity when the target signals a forthcoming movement to the right. Such an activity may then strengthen preparatory activity prior to the next movement.

In fact, this type of behavior can be seen in the activity of neurons in the oculomotor circuit from caudate nucleus to SNpr and colliculus [15]. In a left/right remembered saccade task, neurons that fire in response to movements in the rewarded direction increase their firing rate when a target is presented that indicates a forthcoming movement in the rewarded direction. Conversely, they decrease their rate in response to the same stimulus if the reward is switched to the opposite direction. When the saccades are actually made following the disappearance of the fixation light, their onset latencies are more rapid for movements in the rewarded direction. The suggestion is that increased activity after a cue that indicates the next movement will be rewarded prepares the system for the forthcoming movement, such that response times are improved. Interestingly, the changes in firing pattern and onset latency are not observed in the presence of drugs that block D1 receptors.

3.2. *Dopamine and saliency*

Evidence supporting the role of dopamine as a reward prediction error signal is strong: the dopamine burst declines as situations giving rise to rewarded actions are repeated; bursts of dopamine can transfer to stimuli that predict the presence of a forthcoming reward; and absence of expected reward leads to reduced dopaminergic firing. However, dopaminergic bursts occur not only to reward but also, in novel environments to any unexpected stimulus. In addition, the latency can be short, around 70−100 ms after presentation of the stimulus [16, 17]. In such circumstances, there is no time for the stimulus to have been evaluated and characterized by reward. In fact, no reward may even have occurred by the time of the burst itself.

In such circumstances, it has been proposed that dopamine is signaling the presence of a salient stimulus in the environment.

It has been argued that these qualities of the dopamine signal could be used by the animal to determine the source of the salient event [16]; that is, was it caused by a prior action of the animal or was caused by an external event. If the signal was always associated with a particular behavior of the animal, that behavior is likely to have some causative action and will be reinforced by the dopamine burst. If there is no regular pattern of behavior associated with the burst, no actions are reinforced. The net result is that if the dopamine burst is signaling a salient event, rather than reinforcing action−reward, it will (less specifically) reinforce action− outcome coupling. It will build up a repertoire of knowledge that in specific circumstances, a given action is likely to lead to a certain outcome, irrespective of whether the outcome is rewarded or not.

This can be interpreted as the first stage in constructing an optimal pattern of behavior. First of all, we need to know what the consequences of an action might be, with a second stage then being to determine which consequences are most useful (rewarding). In the saliency scheme, this second stage may be controlled by later arriving signals that have had time to evaluate whether an outcome is good or bad or indifferent. Whether this occurs in a different part of the basal ganglia or in frontal areas of cortex is unknown.

At the present time, the distinction between dopamine's role in reward versus saliency is unresolved. Although the majority of work has tackled the reward hypothesis, it is worth recalling that the experiments in which this is tested are sometimes far removed from a naturalistic setting. Monkeys may make the same movements many thousands of times, often within a highly controlled environment. Perhaps the saliency properties of the dopamine signal would be more important in natural settings.

3.3. *Habitual versus goal-directed action*

In the description above, the basal ganglia operates as a learning machine that associates particular inputs with specific outputs in order to maximize behavioral rewards. In the animal literature, such instrumental learning is often subdivided according to the strength of the link between input and behavior into what are termed goal-directed and habitual behaviors. A habitual behavior is difficult to devalue [5]. A rat might have learned to press a lever in order to obtain a reward. If the animal continues to press the lever even when it is no longer rewarded, its response to the lever is termed habitual; alternatively, if the rat gives up pressing the lever after a few unrewarded trials, it is termed a goal directed response. That is, the rat presses the lever in order to obtain a goal (reward).

These two sorts of learning appear to be represented in slightly different parts of the cortico-basal ganglia−cortex loop. In rodents, lesions of the dorsolateral striatum (corresponding roughly to the posterior putamen in primates) impair habitual

responding while leaving goal-directed responding unaffected. In contrast, lesions of the dorsomedial striatum (corresponding to anterior putamen and caudate in primates) impaired goal-directed behavior but retained habitual responding. A similar effect is seen in monkeys, where posterior putaminal lesions (inactivation with the GABA agonist, muscimol) disrupt well-learned sequences whereas anterior lesions that also involve the caudate affect the acquisition of new sequences [5].

It can be imagined that output from posterior putamen is more likely to target primary motor areas, thus influencing motor outputs more directly that output from anterior putamen and caudate which may target secondary motor areas and more frontal regions of cortex. As learning proceeds, basal ganglia output becomes more and more likely to engage direct motor outputs and provoke automatic (or habitual) responding. There is some evidence that this also occurs in humans during extensive learning of a complex finger-tapping sequence: fMRI studies show initial activation of caudate and anterior putamen which then moves more posteriorly at a stage when subjects can perform the sequence even when they are doing a second task at the same time [18].

3.4. *Stopping: A role for the hyperdirect pathway?*

Although the basal ganglia machinery may usually do a good job of selecting the best movement option given a particular pattern of input, there are occasions when we may need to abort the selected pattern. A green traffic light might have reinforced pressure on the accelerator pedal, but as we approach the road crossing the light may unexpectedly change to red, and we have to stop accelerating and press the brake. There is some evidence the hyperdirect pathway via the STN may play a role in this, and terminate basal ganglia facilitation of movement by generating a rapid global facilitation of the inhibitory output of the GPi/SNpr.

Experiments in monkeys have shown that the unexpected termination of a response produces a burst of activity in the pre-supplementary motor area of cortex that is then followed by activation of STN [19, 20]. If the burst of activity in pre-SMA is delayed, the expected movement fails to be suppressed.

4. The Basal Ganglia and Parkinson's Disease

The most common disease of the basal ganglia is Parkinson's disease, in which there is gradual death (over many years) of dopaminergic neurons of the SNpc and other brainstem areas. Initially, the disease affects dopaminergic projections to posterior putamen, and only later in the disease does the denervation become more widespread. Despite the wealth of new information about the basal ganglia summarized in the models above, the data only help explain one of the three main symptoms of Parkinson's disease. Bradykinesia and associated problems in movement are relatively well addressed by the models, but the causes of tremor and rigidity are still mysterious.

4.1. *History*

Historically, the development of the initial anatomical model (Fig. 1) of information flow in the basal ganglia was an enormous boost for Parkinson's disease. It suggested (on the basis of a series of animal experiments) that loss of the dopaminergic input to striatum would increase the basal discharge of the output nuclei. Indeed, this is the arithmetical result of adding up all the excitatory and inhibitory connections in the direct and indirect pathways that are affected by dopamine. In this view, the "brake" of the basal ganglia would be increased and movements would become more difficult. Experiments in Parkinsonian monkeys treated with the toxin MPTP, which destroys dopaminergic neurons, showed that there was indeed an increase in GPi/SNpr activity consistent with this model. This line of reasoning led to the reintroduction of neurosurgical lesions of the internal pallidum to treat patients with Parkinson's disease. Finally, again according to the model, it was shown that the STN nucleus was also overactive in MPTP-treated monkeys, and that lesions here also alleviated symptoms [21], and this is now a commonly used treatment of late-stage Parkinson's disease.

However, the results of surgery in humans themselves led to a reappraisal of the model. The main observation was that patients with Parkinson's disease who had severe drug-induced dyskinesias (excess involuntary movements associated with changing levels of dopamine that occur after every dose of LDOPA) also improved after pallidotomy. This was unexpected since dyskinesias, or excess movements, were thought to be the result of *reduced* basal ganglia output. Thus, they should have been made worse not better by pallidotomy.

The result was that the rationale for surgical intervention was reassessed. The general consensus now is that lesioning the output of the basal ganglia removes a "noisy" and interfering signal from the motor system. Reducing noise allows the rest of the system to function relatively well, although not as fully as normal. Critically, this reinforces the idea that the basal ganglia is not essential for movement, but that they assist preparation for movement. This particular aspect of basal ganglia function has become the focus of much basal ganglia research at the expense of wider questions that explain symptomatology in basal ganglia diseases [22].

4.2. *Present*

The predominant feature in mild to moderately affected patients when they are studied off their normal dopaminergic therapy is slowness of movement, or bradykinesia. In addition, patients complain that moving requires a lot of effort. At first sight, this would be consistent with failure of the basal ganglia to provide automatic selection of appropriate motor plans which normally prepare the system for action [23]. Presumably patients have to replace this automatic procedure by activity from other parts of the motor system [5]. However, there are two problems with this. First, it is not obvious why movements that had already been learned should be affected by reduced levels of dopamine. After all, in the simple models above,

dopamine is only required for learning; once learned, there is no need for dopaminergic involvement. Second, if the automatic contribution of the basal ganglia has to be replaced by input from other regions, why is it that movements are predominantly slow, rather than simply being delayed?

The first question may indicate that there is a role for tonic as well as phasic levels of dopamine. Indeed, a tonic role seems highly likely in view of the constant, but slow tonic firing rates of the dopaminergic neurons of the SNpc. One possibility is that tonic dopamine controls the overall "gain" of the striatal input-output system [12]; when it is low, the likelihood that an input will recruit the learned pattern of output is reduced whereas if tonic levels of dopamine are high, outputs may be triggered in the presence of minimal input. Patients off therapy would fail to benefit from the automatic selection of appropriate movements, whereas when dopamine levels were restored on therapy, performance would be relatively normal. The same explanation may also account for the excess of movements that are triggered at high levels of dopamine in peak dose levo-dopa–induced dyskinesia. This may well relate to the discussion on rhythms in the basal ganglia below.

The second question is more difficult to resolve. Again, it may relate to the interest in rhythmic activity covered in the section below. However, there may be a second explanation for slowness of movement that relates to the patients' perception of the "cost" of moving fast. In an intriguing experiment, Mazzoni *et al.* [24] asked patients with mild Parkinson's disease to move at various speeds to targets of varying accuracy. They found that patients could move and reach all targets at the required velocity. Furthermore, when they examined those movements that met the speed and accuracy requirement, the patients' performance was just as quick and accurate as healthy volunteers. The difference was that it took the patients more trials to achieve the criterion than the volunteers. That is, even though patients can make fast and accurate movements, they make slower movements while trying to move at the correct speed than healthy individuals.

If patients (at least in the early stages of the disease) are capable of moving quickly and accurately, why do they tend to move slowly? Mazzoni suggested that patients may be more sensitive to the energy cost of moving fast, so that they perceive it more "difficult", or more "effortful" to move fast. For example, it could be that on successful trials, there is a smaller dopamine reward burst in patients and this slows reinforcement of the correct motor output. They have to make more movements to reach criterion than normal. Like healthy subjects, movements are more likely to be slower than criterion than faster since they are energetically less demanding.

4.3. *Rhythmic activity in basal ganglia*

Both single-cell as well as local field potential recordings in many nuclei of basal ganglia and cortex have shown that activity in the cortico-basal ganglia–cortex loops tends to be rhythmic [25, 26]. Populations of neurons in each area tend to oscillate in synchrony giving rise to field potential activity at a variety of different

frequencies. Recordings from deep brain electrodes in human patients with Parkinson's disease suggests these oscillations tend to occur within two main frequency bands, broadly defined as < 30 Hz and > 30 Hz. When patients are withdrawn from therapy for 12 h or so, then the predominant mode is < 30 Hz (usually between 15−30 Hz, termed the beta band); when on therapy, higher frequencies are more common, particularly at the onset or in preparation for movement when they shift into the gamma range (40−70 Hz).

Slow oscillations involve larger subpopulations of neurons than faster rhythms, and it has been suggested that this makes it more difficult for the basal ganglia to shift into different patterns of activity needed for correct selection of movement. Beta activity effectively reduces information capacity of the basal ganglia network. This impairs processing and will reduce basal ganglia contributions to movement.

5. Conclusions

It is clear, even in a short review such as this, that ideas about the function of the basal ganglia are still being developed. However, the predominant ideas revolve around a role in selection of movements based on learned associations with rewarding or successful events. It contrasts, for example, with current views of the role of the cerebellum, which is often seen as adapting movements on the basis of error signals from peripheral and central feedback. The basal ganglia are no longer what the British neurologist Kinnier Wilson once described as the "dark basements" of the brain; but neither have we climbed to the summit of their contribution to movement control.

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NEURAL CIRCUITS OF THE CEREBELLUM: HYPOTHESIS FOR FUNCTION

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The rapid growth of cerebellar research is going to clarify several aspects of cellular and circuit physiology. However, the concepts about cerebellar mechanisms of function are still largely related to clinical observations and to models elaborated before the last discoveries appeared. In this paper, the major issues are revisited, suggesting that previous concepts can now be refined and modified. The cerebellum is fundamentally involved in timing and in controlling the ordered and precise execution of motor sequences. The fast reaction of the cerebellum to the inputs is sustained by specific cellular mechanisms ensuring precision on the millisecond scale. These include burst–burst reconversion in the granular layer and instantaneous frequency modulation on the 100-Hz band in Purkinje and deep cerebellar nuclei cells. Precisely timed signals can be used for perceptron operations in Purkinje cells and to establish appropriate correlations with climbing fiber signals inducing learning at parallel fiber synapses. In the granular layer, plasticity turns out to be instrumental to timing, providing a conceptual solution to the discrepancy between cerebellar learning and timing. The granular layer subcircuit can be tuned by long-term synaptic plasticity and synaptic inhibition to delay the incoming signals over a 100-ms range. For longer sequences, large circuit sections can be entrained into coherent activity in 100-ms cycles. These dynamic aspects, which have not been accounted for by original theories, could in fact represent the essence of cerebellar functioning. It is suggested that the cerebellum can, in this way, operate the realignment of temporally incongruent signals, allowing their binding and pattern recognition in Purkinje cells. The demonstration of these principles, their behavioral relevance and their relationship with internal model theories represent a challenge for future cerebellar research.

Keywords: Cerebellum; motor control; ataxia; timing; LTP; LTD.

1. Introduction

The cerebellum (Fig. 1) represents one of the most intriguing parts of the brain. The cerebellum is present in the most primitive vertebrates and evolves through phylogenesis reaching its maximum expansion in humans. Early functional hypothesis

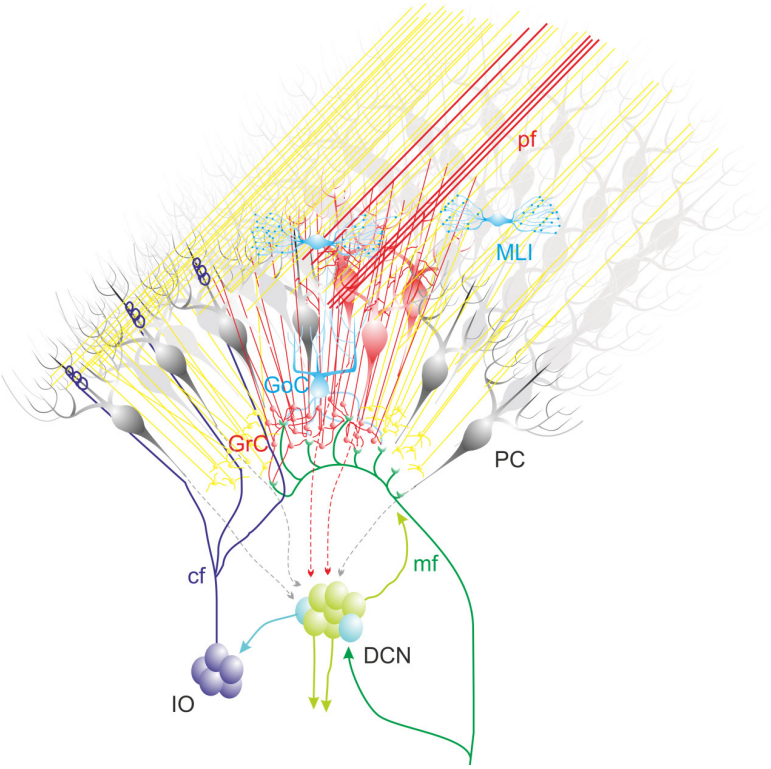

Fig. 1. The cerebellar network. The figure schematically depicts the cerebellar network. The labels indicate: mf, mossy fiber; cf, climbing fiber: pf, parallel fiber; GrC, granule cell; GoC, Golgi cell; PC, Purkinje cell; MLI, molecular layer interneuron; DCN, deep cerebellar nucleus; IO, inferior olive. The figure highlights the activation of a cerebellar module in which a core of active GrCs activates the overlaying PCs and pfs (in red). In a cerebellar module, signals deriving from these PCs go the group of DCN neurons, which was activated by the mf activating the cortical module, and which sends in turn mossy fiber back to this same cortical module in a recurrent loop [73, 142, 189]. Adapted with permission.

on the cerebellum preceded and then coevolved with the histological work of Camillo Golgi and Ramón y Cajal [126, 39]. At the beginning of the 19th century, by using clinical observation and experimental ablation experiments, it was clear that the cerebellum was involved in motor control and coordination leading to the definition of the triad of symptoms still used for clinical diagnosis of cerebellar dysfunction: atonia, asthenia, and astasia. Thereafter, clinical observations from soldiers wounded in the cerebellum during the 1st World War and from patients with cerebellar tumors revealed the association with voluntary tremors and diskinesia, leading to the modern concept of ataxia. Thus, initially, knowledge on the cerebellum was exclusively bound to movement. Only later, the role of cerebellum in coordinating emotional and visceral functions, in making sensory predictions and in elaborating certain aspects of cognition has been supported [93, 70, 16, 157]. In addition, recently, dysfunctions of the cerebellum have also been correlated with cognitive disorders including autism, schizophrenia and dyslexia. Therefore, the

mechanisms of cerebellar functioning have to be viewed in an expanded context, of which motor control is just one important aspect [93, 70, 16, 19]. It is possible that the cerebellum operates through a common mechanism affecting different aspects of behavior in turn. In order to define this mechanism, it is useful to evaluate the most characteristic anatomical and functional properties of the cerebellum.

(1) The cerebellum is connected with the most important structures of the central nervous system, including brain-stem, spinal cord, basal ganglia, limbic system, thalamus and several specific and associative areas of the cerebral cortex. Given the homogeneity of the cellular and circuit organization, these new discoveries imply the existence of a basic cerebellar module (Fig. 1) implementing a "general cerebellar algorhythm". The variety of effects deriving from cerebellar functions has then to depend on the areas to which a certain cerebellar module is connected [7, 24, 73, 142, 189].
(2) The cerebellum is extremely fast and reacts to the inputs in about 10 ms, i.e., 1–2 orders of magnitude faster than the cerebral cortex (this is largely due to the feed-forward rather than recurrent organization of the cerebellar circuit; [17]). Moreover, cerebellar control on movements operates in the millisecond range, reaching a precision unattainable in cerebro-cortical circuits [182]. In this respect, and because of its ability to coordinate movement sequences, the cerebellum has been considered a *timing* machine [62, 61].
(3) The cerebellum is involved in learning implicit memory tasks but, different from the cerebral cortex, it does not retain explicit memory. The cerebellar circuits are capable of strong plastic modifications and can also redirect plasticity toward extracerebellar structures. For this reason, the cerebellum has been considered a *learning* machine [88–90].
(4) The cerebellum has a characteristic double connectivity with central and peripheral structures (Fig. 2). This would allow the cerebellum to compare cortical with sensory patterns, an operation leading to the *sensory prediction* process [93, 95, 94].
(5) The cerebellar cortex shows a complex topology determining multiple *fractured somatotopy* maps, differing from the more linear organization of body parts or sensory features characterizing specific areas of the cerebral cortex (though multiple representations, e.g., of muscles, characterize also the neocortex; [160]). Following the input stage, the signals are propagated through a double vertical and longitudinal organization of fibers. This architecture, together with specific aspects of local neuronal connectivity, is thought to represent the structural basis allowing to process, order and combine complex spatio-temporal sequences [182, 170, 169].
(6) The cerebellum contains about half of the neurons of the whole brain and more neurons than the cerebral cortex (3.6:1) [80] but, differently from the latter, it has little to do with consciousness. Similar to the cerebral cortex organized in columns, the cerebellum is organized in modules. However the cerebellar

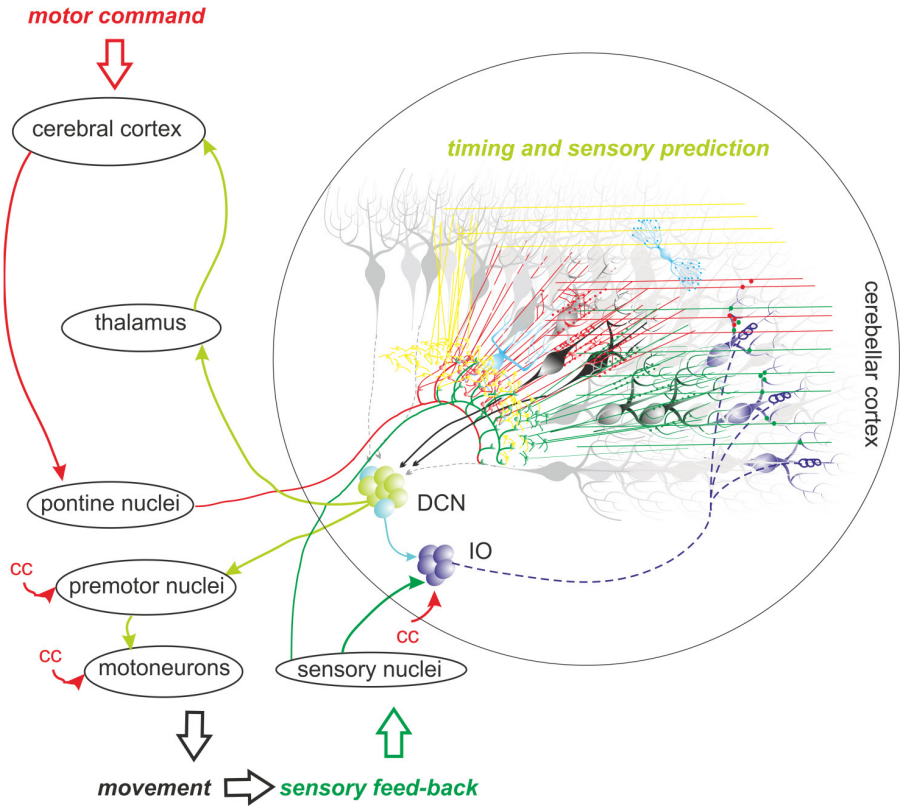

Fig. 2. Cerebellar connectivity. Schematics of the general connectivity of the cerebellum with other brain areas. The cerebellum receives a double innervation from central and peripheral structures. To illustrate the principle, a motor command is generated in the cerebral cortex and, while it is sent to motoneurons, it is also relayed to the cerebellum through the pontine nuclei. Movement generates a sensory feedback, which is sent back to the cerebellum through multiple pathways. Elaboration in cerebellar circuits generates signals transmitted to the deep cerebellar nuclei (DCN) and from there to the thalamo-cortical circuit and to the premotor nuclei of the brain-stem. All these signals enter the cerebellum through the mossy fibers and the granular layer. Another pathway originates from the inferior olive (IO). IO receives sensory and cortical inputs and generates the climbing fiber. The cerebellar circuit redistributes mossy fiber signals along the sagittal axis and the climbing fiber signals along the transverse axis (convergence points are indicated by dots). It should be noted that sensory and cognitive signals could be transmitted, as well as motor commands, along multiple descending pathways reaching various parts of the cerebellar cortex.

modules have relatively weak recurrent connectivity and interconnectivity compared to cortical columns, a fact that has been invoked to explain the marginal implication of the cerebellum in conscious percepts [183, 23].

It is clear that these functional observations do not always find correspondence with symptoms caused by cerebellar dysfunction (which nonetheless have had large application and importance in clinical practice). A new approach to the cerebellum has to include, on one hand, a definition of the fundamental operations that the cerebellum performs and, on the other hand, a detailed investigation of the cellular properties of the circuit. In this paper, I will consider how the current concepts and

observations on cerebellar functions can be reconciled, integrated and extended through recent evidence on cerebellar neurons and network and on cerebellar connectivity.

2. The Cerebellum and Brain Activity

In order to interpret the complex set of neurophysiological and neuropathological data related to the cerebellum, a conceptual framework is required including the principles of cerebro-cerebellar interaction. Brain activity elaborated in the thalamo-cortical circuits, by exploiting internal memories, continuously generates an internal representation that is then compared with the objective world [95, 23, 71, 156, 143]. This operation is assisted by subcortical loops involving the cerebellum, which, by using its own internal memories and a broad set of afferent signals, informs the cortex in a feedback loop about the correctness of predictions [90]. These cortico-cerebellar loops, by improving the identification of errors and novelty (*sensory prediction*), can trigger automatic corrections, promote learning and redirect attention. This operation is probably part of a more general strategy. The cortex, given the slow elaboration times, the randomness affecting activity in recurrent neuronal assemblies and the incomplete predictability of controlled systems reactions [23], is thought to generate crude commands, which need to be refined, ordered and sorted. These operations are thought to require the precise *timing* and *learning* capabilities of the cerebellum [37]. Dysfunction in these mechanisms and loops would be the ultimate cause of several pathological states. In summary, the function of the cerebellum could be conceived not just for its motor consequences but, more generally, within the framework of high-level cognitive processing controlling the correctness of internal brain predictions with respect to the evolution of states in the environment and in the body and brain itself.

2.1. *Cerebellar connections and functions*

Different parts of the cerebellum contribute to distinct behavioral aspects. The vestibulo-cerebellum, constituted by the flocculo-nodular lobe, regulates equilibrium and vestibulo-ocular reflexes: it receives mostly vestibular and ocular inputs. The spino-cerebellum, including the vermis and the intermediate part of hemispheres, is involved in movement execution including feedback adjustments; it receives somatosensory, labyrinthine, visual and auditory input. The cerebro-cerebellum, represented by the lateral part of the cerebellar hemispheres, plays an important role in preparation, initiation and timing of motor acts via the dentate nuclei; its principal inputs arise from the premotor and posterior parietal cortex. Prominent among these connections, are the loops involving the cortico-cerebellar oculomotor system [73, 72]. Moreover, the association and limbic areas are largely connected with the posterior lobe of the cerebellum, in particular crus I and II.

Reciprocal connections appear to transmit information through the cortico-nuclear microcomplex to the deep cerebellar nuclei and from there to the thalamus and back to the cerebral cortex [99, 104, 145]. By maintaining a similar anatomic organization in all its parts, the cerebellum could organize and modulate cognition and emotion in a similar way as it organizes and modulates motor coordination and control. Accordingly, cerebellar alterations affecting the cerebello-cortical loops may lead not only to motor abnormalities but also to behavioral, cognitive and affective alterations. The cerebellum is fundamental for contextualizing specific stimuli and coordinating their spatio-temporal evolution, generating coherent ensemble activities [93, 95, 94]. Therefore, dysfunction of the cerebellar circuits and of information reentry toward the frontal and parietal cortex may contribute to preventing the formation of coherent and contextualized behaviors. Additionally, the cerebellum is critical for revealing differences (either error or novelty) between predictions elaborated by the cortex and the stimuli conveyed by the senses. Thus, dysfunction of the cortico-cerebellar circuits may prevent the detection of novelty and impair attention switching [93, 95, 94, 4, 5, 33, 132].

2.2. *Cerebellar dysfunction*

Cerebellar ataxia (from Greek α-$\tau\acute{\alpha}\xi\iota\varsigma$, meaning "lack of order") [36] is expressed through a variety of elementary neurological deficits, such as antagonist hypotonia, asynergy, dysmetria, dyschronometria, and dysdiadochokinesia. In a very general description, (1) dysfunction of the vestibulocerebellum impairs body balance (Romberg test) and the control of eye movements (saccade alterations, nystagmus), (2) dysfunction of the spinocerebellum impairs gait (wide-based "drunken sailor" gait, characterized by uncertain start and stop, lateral deviations, and unequal steps), (3) dysfunction of the cerebrocerebellum causes disturbances in carrying out voluntary, planned movements. These disturbances include intention tremor (coarse trembling, accentuated over the execution of voluntary movements, possibly involving the head and eyes as well as the limbs and torso), peculiar writing abnormalities (large, unequal letters, irregular underlining), a peculiar pattern of dysarthria (slurred speech, sometimes characterized by explosive variations in voice intensity despite a regular rhythm). Finally, a less known sign is the so called "dysmetria of thought", which arises as a consequence of the damage of the cortico-cerebellar connections relating the cerebellum to prefrontal and limbic areas. This disturbance configures the *cerebellar cognitive-affective syndrome* (CCAS) [159]. CCAS is characterized by: (1) disturbances of executive functions, which include deficient planning, set-shifting, abstract reasoning, working memory, and decreased verbal fluency; (2) impaired spatial cognition, including visual-spatial disorganization and impaired visual-spatial memory; (3) personality change characterized by flattening or blunting of affect and disinhibited or inappropriate behavior; and (4) linguistic difficulties, including disprosodia, agrammatism and mild anomia. The net effect of these cognitive disturbances is a general lowering of overall intellectual performance resembling a prefrontal syndrome.

3. The Cerebellum and Motor Control: Theories and Models

The cerebellum has inspired some amongst the most renown theories and models of brain functioning. These have played an important role in fueling discussion and stimulating research on cerebellar mechanisms of function.

3.1. *Early theoretical models*

The first insight on how the cerebellum might work, came both from the realization that it is involved in motor control and from anatomical analysis and electrophysiological recordings *in vivo*. These showed that the cerebellum forms a large inhibitory loop controlling the deep cerebellar nuclei, in which excitation is conveyed to Purkinje cells through the mossy fiber−granule cell−parallel fiber pathway and the inferior olive−climbing fiber pathway (Fig. 2) [62, 137, 92, 60]. Then it was found that all the neurons in the cerebellar cortex are inhibitory, with the exception of the granule cells. The reaction times of the cellular elements to peripheral stimulation were reported [61]. These ideas were synthesized by two main theories: Eccles proposed the *beam theory* [61, 62] and Marr and Albus the *motor learning theory* [123, 3, 67]. Later on, Ito developed the *forward controller theory* [88, 90, 87], which considers the cerebellar function in the context of motor system control (see below). Since then, the view of how the cerebellum operates has been focused on three main concepts: (1) the cerebellum operates by decorrelating the inputs and controlling gain in the granular layer and by detecting known patterns in Purkinje cells; (2) pattern recognition in Purkinje cells is regulated by memory storage at the parallel fiber−Purkinje cell synapse under climbing-fiber control; (3) when unfamiliar patterns are detected, the Purkinje cells change their firing rate and regulate activity in the deep cerebellar nuclei, which then emits the correction signals required to control behavior. Under a different perspective, the *parallel fiber timing hypothesis* maintained that different delays in parallel fiber activity would be critical for explaining cerebellar functioning [20]. Although conduction delays are probably marginal, the timing issue is relevant and has been supported recently by electrophysiological data and cognitive experiments. Other more abstract approaches have also been developed. The mathematical foundations of the Marr-Albus-Ito hypothesis have been investigated through the *adaptable filter theory* (for a review, see [50]). The *tensor network theory* implies that the cerebellum acts as a metric tensor establishing a geometry for the central nervous system motor hyperspace [140].

3.2. *The motor control models*

From the engineering view point, the cerebellum has been supposed to provide the key to resolve the problem of multi-dimensional nonlinear control required for regulating movement [89, 83, 82, 81, 103, 165, 168, 195]. Thus, understanding the cerebellum has been turned into the problem of controlling non−stiff-joint "plants".

Motor control theories are based on the general connectivity of the cerebellum (Fig. 2) making broad assumptions on its internal microcircuits [166]. When the cortex sends signals to motoneurons in the brain stem and spinal cord, it also sends a copy of this message to the cerebellum (Fig. 2). In addition, information arrives to the cerebellum from muscle spindles, joints and tendons. Therefore, the cerebellum receives both motor commands and sensory signals. This allows extracting corrective models on the "plant" (the ensemble of joints, muscles, and forces) for accurate movements (internal models are dealt with in detail by Amir Karniel in this issue). Traditionally, feedback from an internal model of the "plant" has been used to generate a *forward model* able to predict the dynamics of muscles from the state of the system and to compute a controller output. The natural error signal for learning motor commands is the difference between actual and correct commands (motor error). By considering the possibility that the cerebellum adds corrective signals on the sensory rather than motor signals, it has been proposed a cerebellar control loop called *recurrent model*. In autonomous systems, the correct command is typically unknown. Only information about the sensory consequences of incorrect commands is available, which leads to an error representation based on sensory signals. Both the forward and recurrent models have been proposed as biologically plausible to explain cerebellar motor control functions and may indeed develop a complementary functionality. Experimental evidence locating forward models in the cerebellum has been provided using modeling, fMRI studies [82, 54] and TMS [32, 31].

3.3. *From theoretical to computational models*

Clearly, while theoretical models are appealing for their conceptual simplicity and can help resolve certain computational problems in motor control, they have very poor biological details and do not help in explaining how the cerebellar network operates. In the last decades, experimental data have suggested indeed that the cerebellum operates in a much more complex manner than predicted by available theories. One of the major issue is that of spatio-temporal dynamics, whose description based on anatomical observations proved insufficient. Schematically, (1) the mechanisms of the granular layer go far beyond simple decorrelation [38], (2) long-term synaptic plasticity does not occur only in the parallel fibers [38, 76], (3) the inferior olive operates as a complex timing system and not simply to control Purkinje cell plasticity [97]. Moreover, the cerebellar neurons without any exceptions, and especially the Purkinje cells and the deep cerebellar nuclei cells, (4) have operative states that go far beyond the concept of firing rate regulation [96] (see below). This means that knowledge on the functioning of neuronal networks of the cerebellum is insufficient at the very least, and that new experimental and computational tools are needed to investigate cerebellar network function and dynamics. Recently, a new generation of computational models has appeared. In these models, neuronal properties are explicitly implemented highlighting the contribution of single cell and synaptic dynamics [176, 127, 107, 118]. The gain of

this approach is realism in neuronal computation, the loss is a high complexity in circuit functions: a further synthesis and abstraction process is then required to reconcile computation with a general theoretical framework. A convenient approach is provided by the Adaptable Filter Theory [51], which can incorporate salient experimental properties of the network and reinterpret the results of the realistic computational models.

4. The Neurons and Network of the Cerebellum

The cerebellar network can be subdivided into four main sections: the granular layer, the molecular layer, the deep-cerebellar nuclei, and the inferior olive [88, 89, 137, 62, 8]. The molecular and granular layer form the cortical part of the cerebellum. The deep cerebellar nuclei complex, which is part of the precerebellar nuclei, represents the only output pathway of the cerebellar cortex. Signals are then conveyed to various brain-stem nuclei (notably the reticular nucleus and the red nucleus) and to the antero-lateral thalamus, through which signals are conveyed to the controlateral cortex. The inferior olive complex is the only source of climbing fibers, while various precerebellar nuclei and spinal cord centers generate the mossy fibers. The general organization of the cerebellar input−output relationships is depicted in Fig. 2.

4.1. *Structure and function of the granular layer*

The granular layer is composed of three main types of neurons: the granule cells, the Golgi cells and the Lugaro cells. In the vestibulo cerebellum, a fourth type is represented by the UBCs. The mossy fibers make excitatory glutamatergic synapses with all these cell types (the connection with Lugaro cells is not yet well defined; Michael Hausser, personal communication). The Golgi cells make inhibitory connections to granule cells (and UBCs) and the UBCs inhibit the Golgi cells. Connections between climbing fibers and Golgi cells have also been reported on morphological basis, although functional determinations are still poor (Galliano and De Zeeuw, personal communication).

The mossy fibers provide the only excitatory input to granule cells (and to UBCs, which activate other UBCs or granule cells). The granule cells, are the only neurons sending excitatory outputs to the Purkinje cells and to the molecular layer interneurons (the granule cells and UBCs are also the only excitatory neurons of the cerebellar cortex as a whole). In turn, the Golgi cells provide the only inhibitory input to the granule cells generating a complex combination of feed-forward, feedback and lateral inhibition effects (see [69] for review). Importantly, the Golgi cell inhibitory axons extend far apart from their input field, causing a massive lateral inhibition. This effect has been largely investigated and documented. Functionally, the circuit seems designed to allow a massive spatio-temporal reconfiguration of the

input, with several control mechanisms provided by local connectivity, long-term synaptic plasticity, intrinsic excitability and neuromulatory systems.

This seemingly simple circuit contains about half of the neurons of the whole brain and has inspired several functional theories. The combinatorial organization of the granular layer [123] has inspired the hypothesis of signal decorrelation. This hypothesis originated from the observation that granule cells are much more numerous of the mossy fibers. Therefore, signals could diverge over many more lines than in the input, allowing decorrelation of common components.

The granular layer has been recently shown to transform incoming signals by making use of specific cellular mechanisms controlling excitation, inhibition, oscillation and plasticity [37, 65, 35]. The mossy fibers generate spike bursts following punctuate sensory stimulation [25, 100, 147]. The analysis of responses to such bursts has inspired numerous subsequent developments.

(i) By virtue of Golgi cell lateral inhibition, the granular layer response to mossy fiber bursts are spatially organized in center-surround, where excitation prevails in the center and by inhibition in the surrounding areas [120]. It has been recently shown that sensory stimuli (punctate facial stimulation) activate dense clusters of granule cells amounting to about 600 units, and that the clusters activated by sensory fibers and by cortico-pontine fibers are separated [56]. The percentage of spiking granule cells can vary from 2% to over 20% depending on the presence of LTD or LTP in the cluster. In response to the same inputs, localized activation of the Golgi cells can also be observed [56, 181].

(ii) By virtue of Golgi cell feed-forward inhibition, the granular layer generates a time-window effect limiting the duration and intensity of the output [37, 133].

(iii) By exploiting specific properties of NMDA and GABA receptors, the granular layer behaves as a high-pass filter allowing patterns over 50 Hz to be optimally transmitted [121].

(iv) By exploiting extended feedback inhibition through Golgi cells, the granular layer can sustain coherent oscillations [118] synchronizing large granule cell fields [139, 77]. Synchronous oscillations were also shown to exploit electrical junctions between Golgi cells [58]. The oscillations are enhanced when bursts are conveyed in the theta-frequency band due intrinsic cellular resonance [40, 174, 175].

(v) In response to specific burst patterns, the granular layer generates long-term synaptic plasticity at the mossy fiber — granule cell synapse. Since induction is regulated by synaptic inhibition (which controls membrane depolarization and therefore the level on NMDA channel unblock and calcium influx), LTP dominates in the center and LTD in the surround of the response fields, consolidating specific geometries of activity.

(vi) Finally, without requiring the burst activity regime, the granular layer can operate gain control operations exploiting tonic inhibition in the glomerulus [128].

But how do these mechanisms contribute to signal decorrelation and to help extend our understanding of cerebellar functioning? Using a realistic computational model of the granular layer [176], it has been possible to evaluate the impact of cellular and synaptic dynamics on circuit computations. Burst stimulation of a small mossy fiber bundle results in granule cell bursts delimited in time (time-windowing) and space (center-surround) by network inhibition. This burst−burst transmission shows marked frequency-dependence configuring a high-pass filter with a cutoff frequency around 100 Hz. The contrast between center and surround properties is regulated by the excitatory−inhibitory balance. The stronger excitation makes the center more responsive to 10−50 Hz input frequencies and enhances the granule cell output (with spike occurring earlier and with higher frequency and number) compared to the surround. Synaptic plasticity at the mossy fiber−granule cell relay, by exploiting changes in neurotransmitter cycling, can fine tune the transmission properties of the center-surround structure. The center, by generating LTP, reacts to spikes bursts over a broader input frequency range emitting new bursts with shorter delay and higher number of spikes compared to the surround (which is dominated by LTD). Interestingly, the plastic mechanisms revealed *in vitro* can explain LTP and LTD *in vivo*, concentrating the firing granule cells in the center and increasing inhibition in the surround [56].

An emerging novel hypothesis is that the granular layer network behaves as a complex set of filters operating in the space, time and frequency domains, and that this filter can be adapted through long-term synaptic plasticity and coordinated by theta-frequency oscillations. Thus, the original idea of input decorrelation may be extended to temporal dynamics of circuit activity and in particular to spike timing, an aspect that deserves future investigations.

4.2. *Transmission of signals from granular to molecular layer*

The signal generated by the granular layer consist of complex sequences of spikes in granule cells, which need then to be transmitted to the molecular layer. The parallel fibers, after dividing into two opposite branches originating from the ascending axon of granule cells, travel transversally for millimeters contacting numerous Purkinje cells. This characteristic organization has inspired the idea that signals generated by granule cells are conveyed along the parallel fibers activating beams of Purkinje cells (the "Beam Theory": [62, 20]. Activation of beams is indeed observed using parallel fiber stimulation (e.g., see [190, 11]. However, punctuate stimulation *in vivo* causes a prominent vertical activation of Purkinje cells overlaying the active granular layer areas [19, 30, 117, 78, 152]. A possible explanation was that vertical activation could reflect either differential synaptic density or strength or differential spike delays along the ascending granule cell axon compared to parallel fiber synapses. It was originally assumed that the difference was not in strength but rather in the timing of the inputs in individual synapses of both types [113, 112]. This hypothesis was supported by the demonstration of the functional equivalence of the two inputs [191,

84], although differences in terms of long-term synaptic plasticity have been reported [171, 172]. Alternatively, differential properties of synaptic inhibition could be critical [63, 141, 129].

Clearly, solving the issue also depends on the development of appropriate recording and analysis methods. For instance, initially voltage-sensitive dye recordings did not allow one to determine the specific cellular components contributing to the signals (e.g., [30] while a more strict correspondence has recently been achieved with high resolution techniques and simultaneous imaging-patch clamp recordings in sagittal and coronal slices [121, 122]. These investigations have revealed that optimal responses to mossy fiber input trains occurred for input frequencies over ∼50 Hz in the granular layer and over ∼100 Hz in the overlaying Purkinje cells. Conversely, Purkinje cell excitation along the parallel fibers occurred already at low frequency (<10 Hz) and did not improve with input frequency. The efficacy of GABA-A receptor-dependent inhibition increased passing from the granular to molecular layer and explained the different frequency-dependent responses in these subcircuits. Thus, while molecular layer mechanisms could enhance vertical transmission of high-frequency bursts, inhibitory systems in the molecular layer would prevent diffusion of such amplified responses along the parallel fibers. This result indicates that both spots and beams of excitation can coexist although with different dynamic properties. It should be noted that another mechanism proposed to regulate gain at the mossy fiber — granule cell relay is based on tonic inhibition in the glomerulus [128, 9]. This, however, may not be sensitive to rapid frequency changes between or during bursts (Fig. 3).

A related issue is that granule cells generate their spikes in the initial segment and these invade the whole ascending axon almost instantaneously, so that delay times are abolished in this circuit section [57]. Generation of spike delays in granule cells through long-term synaptic plasticity, Golgi cell inhibition and time-windowing is therefore the most relevant process controlling the temporal information flow toward Purkinje cells. It should be noted that different delays are expected in the different parts of the center-surround structures of the granular layer [56], thus determining the geometry of activation of the molecular layer.

4.2.1. *The molecular layer and Purkinje cell firing dynamics*

The Purkinje cells are the biggest and probably the most complex neurons of the cerebellar cortex. The Purkinje cells are critical for cerebellar functioning and have catalyzed scientific interest about their mechanisms. The Purkinje cells respond with precision of few milliseconds in relation to the initiation and termination of movement (e.g., a saccade; [134, 102, 136, 135]) and movement itself can be controlled on this same time scale [182]. The Purkinje cells collect signals generated from about 200,000 granule cells and are therefore suited for integrating information pre-ordered and pre-elaborated by the granular layer. In this sense, the Purkinje cells have been supposed to operate as perceptrons [22]. Moreover, the Purkinje cells receive input from a single climbing fiber relaying signals from the inferior olive. The

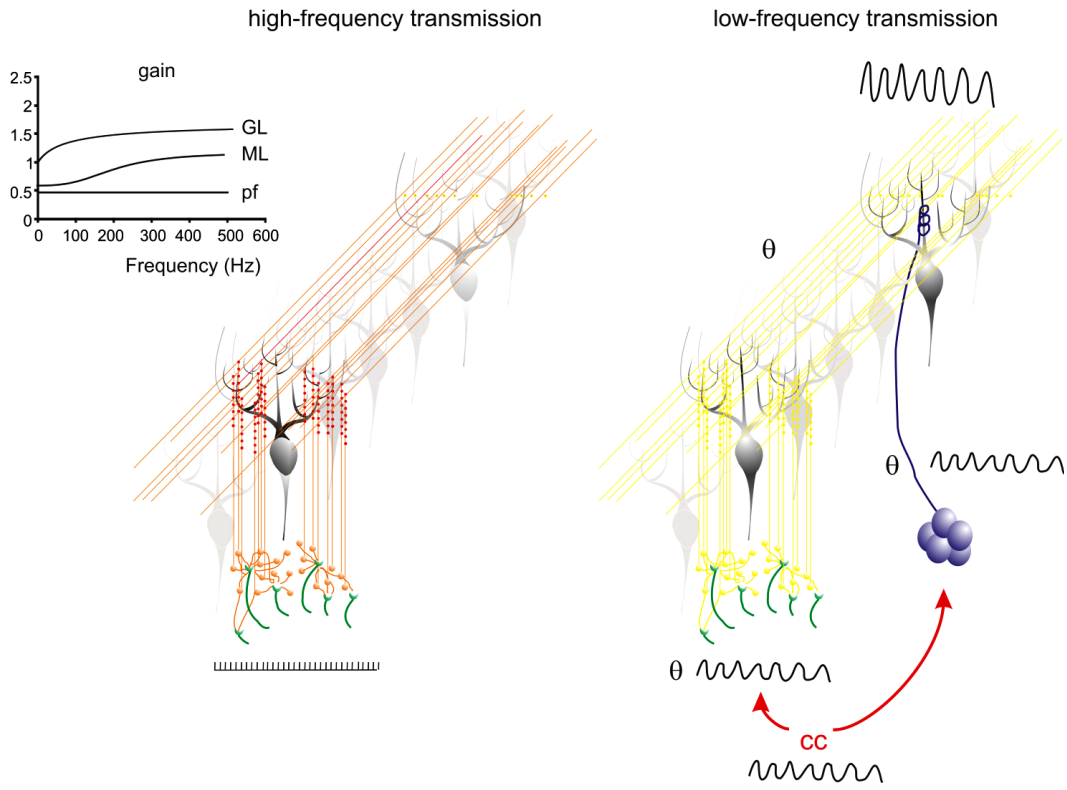

Fig. 3. Hypotheses on signal spread through the cerebellar network. The figure illustrates the spread of signals arriving to the cerebellar network at different frequencies. High-frequency signals, like the bursts conveyed through mossy fibers, are amplified along vertical transmission lines but filtered along the parallel fiber beams. Conversely, low-frequency signals, like those generated by cerebro-cortical oscillations and conveyed to the cerebellum through descending pathways [154, 124], are similarly transmitted along the vertical lines and the beams [122]. It is envisaged that low-frequency signals travelling along the beams would coincide with those generated by the IO in certain Purkinje cells causing local resonant responses.

Purkinje cells has therefore two different kinds of inputs generating simple and complex spikes in response to parallel fiber and climbing fiber activity [61–64]. These neurons generate a rich repertoire of electroresponsive properties including pacemaking, bursting, rebounds, pauses and bistability [113, 112, 193, 179]. While these fundamental aspects have been revealed quite early, the mechanisms through which Purkinje cells process incoming signals have revealed unexpected complexity and are not yet fully clarified.

The Purkinje cells are composed of two main morpho-functional compartments. Parallel and climbing synaptic inputs, as well as those coming from molecular layer interneurons, impinge on a large dendritic tree generating local synaptic responses [110]. Both complex and simple spikes, in turn, have recently been shown to originate from the first node of Ranvier [6, 28, 42, 131, 138]. It is therefore critical to understand how these two cellular sections communicate their electrical signals.

Double-patch recordings and imaging techniques combined with computational modeling have revealed that, while synaptic potentials generated in the dendritic tree can easily reach the soma, spikes generated in the axon cannot travel efficiently into the dendritic tree because of the filtering properties of the structure. The two sections seem therefore to operate separately, with a dendritic portion working as an almost linear integrator without much interference from the spike generation mechanism [141]. The dendritic tree can, however, make use of climbing fiber signals to generate local calcium waves that have a relevant role for generation of synaptic plasticity [42]. Thus, different from cortical pyramidal cells, the firing state of the neuron cannot influence plasticity by itself, which is otherwise controlled (in particular parallel fiber — Purkinje cells LTD, see below) through an independent regulation of intracellular calcium in the dendrites by the climbing fibers [179, 129, 146].

The Purkinje cells express a complex set of ionic channels determining specific excitable properties. Some of the most recent and relevant observations are reported here. The Na^+ channels, in addition to the transient and persistent current, generate a resurgent current favoring complex spike generation [105, 144]. The T-type Ca^{2+} channels regulate complex spike generation as well as controlling intracellular Ca^{2+} [198, 86] along with the P-type Ca^{2+} channels [184]. The role of the H-current in bistability [193, 6] has been recognized. Membrane potential can switch between two stable levels, UP and DOWN, and this transition is regulated by serotonergic modulation of the H-current [193]. Synaptic inputs (either excitatory from parallel and climbing fibers or inhibitory from molecular layer interneurons) can also bidirectionally shift the Purkinje cell states [153] and corticotropin releasing factor (CRF) has a significant impact on the ease and rapidity of the state transitions (Yarom, personal communication; see [91] for a review of neuromodulators affecting cerebellar functioning). Eventually, firing of simple spikes occurs exclusively during the depolarized state. Finally, Ca^{2+}-dependent K^+ channels have been shown to play an important role in controlling the burst-pause behavior of the Purkinje cell [149, 26] along with inhibition coming from molecular layer interneurons. Attempts at explaining the combined effect of ionic channels unequally distributed over various compartments and of the interaction with synaptic inputs and intracellular Ca^{2+} concentration have been carried out by developing multicompartmental models [179, 45, 44, 177].

The activity of Purkinje cells is strongly influenced by molecular layer interneurons, the stellate and basket cells [17, 158, 18]. These neurons operate in feedforward mode and can limit in time and space (through lateral inhibition) the response of the Purkinje cells. These neurons are almost equivalent for their firing pattern (which is also very similar to that of Golgi cells), but stellate cells lay in the higher part of the molecular layer contacting Purkinje cell dendrites with multiple small contacts, while basket cells lay in the lower part of the molecular layer surrounding the Purkinje cell soma with a large basket like synapse. Therefore, stellate cells have been thought to be more suitable for regulating dendritic integration while

basket cell to efficiently regulate the spike output. In a model reconstruction including molecular layer interneuron connections to the Purkinje cell dendrites, beams of activity caused by parallel fibers activity occurred only when inhibition was blocked without remarkably affecting Purkinje cell excitability. Therefore, it has been suggested that feed-forward cortical inhibition can regulate the excitability of the Purkinje cell dendrite without directly influencing the Purkinje cell spiking output independent from synapse location [158]. This act is again a reflection of the electroresponsive organization of the Purkinje cell, since shunting synaptic current in the dendrite or in the soma does not make much difference, since in both cases these currents cannot reach the initial segment and activate spike generation therein.

Another relevant issue is that, while the synapse between parallel fibers and molecular layer interneuron is highly efficient and usually shows short-term depression, the synapse between parallel fibers and Purkinje cells is weaker and shows short-term facilitation [171, 172, 12, 173]. Therefore, single stimuli transmitted from granule cells at low frequency are likely to excite the molecular layer interneurons better than the Purkinje cells, which requires short bursts to transmit efficiently. These properties, combined with the spatial distribution of molecular layer interneuron inhibition, indicates that the molecular layer can exert profound filtering effects on incoming signals determining a large variety of patterns. Long-term synaptic plasticity in the molecular layer interneuron network could further design and stabilize these patterns (see below) sculpting the landscape of Purkinje cell activation.

In summary, available results provide a framework for a functional hypothesis on how the Purkinje cells and molecular layer operate. The Purkinje cells are continuously active because of their intrinsic pacemaking, whose average firing rate can be modulated by parallel fiber activity. Inputs from specific input channels of the granular layer can modify this activity state through impulsive inputs conveyed along the ascending axon synapses generating burst-pause responses [179]. Multiples of such inputs, once integrated over the dendritic tree, can appear as changes in spike variance, as indeed revealed in awake animals during specific behavioral tests [37, 48, 164]. Purkinje cells bistability [193, 116] could provide an additional element of control [164, 197], potentially extending the integration time window to longer times. The action of Purkinje cells is limited in time and space by activity in the molecular layer interneuron network, which can therefore substantially regulate the output of Purkinje cells [130]. The Purkinje cells and molecular layer interneuron synapses can be modified by long-term synaptic plasticity, as considered below.

4.2.2. *The deep cerebellar nuclei and the cerebellar output*

The cells of deep cerebellar nuclei finally convert the activity of microzones into the cerebellar output. The deep cerebellar nuclei are at a key location within the cerebellar network [194]. All of the afferent pathways to the cerebellar cortex make collateral connections on to neurons of the deep cerebellar nuclei (both mossy fiber

and to a lesser extent climbing fiber), while the main output of the cerebellum is formed by the deep cerebellar nuclei projection neurons [13, 186]. In the deep cerebellar nuclei cells, intrinsic dynamics generate subthreshold oscillations, silent pauses and possibly rebound excitation, producing alternating phases of activity [27, 111, 98, 180, 1, 106]. Despite this knowledge, the role of deep cerebellar nuclei in cerebellar computation is largely unclear or controversial [185].

A classical view was that the deep cerebellar nuclei simply acts as a "relay station" between cerebellar mossy fiber (MF) input and cerebellar output to premotor areas, either directly ("direct pathway") or via the cerebellar cortex ("indirect pathway"). This concept has been challenged by three main observations. First, deep cerebellar nuclei neurons inhibit the inferior olive cells regulating their coupling [53] and can therefore take part in controlling the whole inferior olive-deep cerebellar nuclei−Purkinje cell loop [97]. The disruption of this system would be an important cause of ataxia [26, 109]. Secondly, collaterals of deep cerebellar nuclei axons can travel back to the granular layer and generate closed-loop oscillations [38, 107]. Rebound excitation could help maintaining activity in the theta-frequency range. Thirdly, the deep cerebellar nuclei may act as a substrate for motor memory storage [76, 2, 163]. The demonstrations of mechanisms which cause modification of synaptic strength and active membrane properties support this latter viewpoint (see below). The role of rebound excitation in driving plasticity and circuit oscillations is not yet fully resolved.

In addition to these possible roles in cerebellar memory, it appears likely that the neuronal network within the deep cerebellar nuclei processes sensory and motor information in "real-time" but very little is known about the computational functions of the deep cerebellar nuclei, particularly with respect to the role of specific cell types. Indeed, morphological and electrophysiological studies have revealed that the deep cerebellar nuclei consists of diverse neuronal populations with distinct integrative properties [185]. Thus, one can hypothesize that the synchronous oscillations in the Purkinje cell activities together with plasticity at the mossy fiber — deep cerebellar nuclei and the Purkinje cell — deep cerebellar nuclei synapses form the main mechanistic tools to control the activity in the deep cerebellar nuclei output neurons, and that different sets of neurons in the deep cerebellar nuclei are sensitive for oscillations at different frequency ranges [194].

4.2.3. *The olivo-cerebellar loop*

By considering the different anatomical origin of parallel fibers and climbing fibers and their double innervation of Purkinje cell, it was assumed that climbing fibers, originating from the inferior olive, play a fundamental role in motor learning [92, 123, 3]. This contrast between the convergence of a single climbing fiber per Purkinje cell and the massive number of parallel fiber inputs provided the sole basis for the Marr-Albus theory [88]. However, soon thereafter new insight arose from the investigation of neuronal dynamics leading to an alternative hypothesis: the olivo-cerebellar loop may work as a timer for motor activity [114, 192].

Recently this alternative hypothesis has been expanded, considering the olivocerebellar loop as a generator of temporal patterns [97, 96, 196, 115]. This hypothesis postulates that the temporal patterns are encoded in the complex-spike trains, and is based on three assumptions supported by experimental evidence: (1) Inferior olivary neurons form a network of electrically coupled cells, where the coupling is modulated by inhibitory input from the deep cerebellar nuclei. Only in a network configuration, the neurons generate propagating waves of subthreshold oscillations. (2) The electrical synapses in the inferior olive operate only in the absence of inhibitory input from the deep cerebellar nuclei. Hence, olivary networks are dynamically and continuously reassembled by the activity pattern of the GABAergic projection neurons of the deep cerebellar nuclei [96, 27, 53, 187, 125]. (3) Cerebellar Purkinje cells display complex dynamics of spiking activity, suggesting that a request for specific patterns delivered via the mossy fiber system is translated into patterns of olivary activity, which can in turn reorganize activity in specific sections of the cerebellar cortex by sending climbing fiber signals to Purkinje cell organized in sagittal bands [97, 196].

4.2.4. *Cerebellar long-term synaptic plasticity*

Marr [123] and Albus [3] predicted that cerebellar learning should occur with some form of plasticity between parallel fibers and Purkinje cells under control of climbing fibers. The climbing fibers originating from the inferior olive were assumed to play the role of a teacher, instructing the cerebellar cortex to modify its connectivity in order to cope with new motor demands. Parallel fiber−Purkinje cell "LTP" was predicted by Marr and reversed into "LTD" by Albus: LTD was in fact discovered more than a decade later by Ito [92]. The resonance of this discovery can be compared to that of LTP in the hippocampus [15], which followed Hebb's postulate on brain plasticity [79].

In 1984, Eccles said: "For me the most significant property of the cerebellar circuitry would be its plastic ability, whereby it can participate in motor learning, that is the acquisition of skills. This immense neuronal machine with the double innervation of Purkinje cells begins to make sense if it plays a key role in motor learning... it could be optimistically predicted that the manner of operation of the cerebellum in movement and posture would soon be known in principle" (from the foreword to [88]). For more than a decade, the dominant idea had been that LTD was not just the most important but also probably the only relevant form of plasticity in the cerebellum. For instance, Marr [123] explicitly negated the possibility that mossy fiber−granule cell synaptic weights could be modified by activity. He noted that "sooner or later all weights would be saturated" and so plasticity would be unuseful. The Marr's model does not include any mf-grc synaptic plasticity (nor any plasticity at other synapses), although the subsequent extension due to Albus [3] is more permissive. However, this view was challenged by new experimental facts.

Although parallel fiber LTD can be robustly reproduced *in vitro*, its demonstration *in vivo* has remained partial and its involvement in physiologically relevant behaviors has been questioned [163, 148, 43, 29, 49]. In turn, several novel forms of plasticity have been demonstrated. Taking the move from the consideration that NMDA receptors, the main responsible of LTP induction in the brain [14], are abundantly expressed in granule cells, experiments were undertaken demonstrating that LTP can indeed be generated by mossy fiber bursts at the mossy fiber−granule cell synapse [41, 10]. In addition to LTP, mossy fiber−granule cell LTD was also demonstrated. LTP and LTD were related through a bidirectional learning rule based on intracellular calcium concentration changes driven by NMDA receptors [68, 52, 150] and showed a reciprocal spatial distribution [120] preventing the detrimental "saturation" of plasticity predicted by Marr. Even more significantly, LTP and LTD could be demonstrated in the granular layer *in vivo* following patterned tactile stimulation [150] and their mechanism was shown to correspond to that expected from experiments *in vitro* [56]. Once appropriately implemented into a model based on the Marr-Albus-Ito theory, mossy fiber−granule cell LTP and LTD proved able to improve motor learning and performance [166, 108].

Mossy fiber−granule cell LTP was the first form of cerebellar long-term synaptic plasticity to be demonstrated following parallel fiber−Purkinje cell LTD. This finding was soon followed by numerous others revealing novel forms of plasticity at the parallel fiber−Purkinje cell synapse and at the Purkinje cell−deep cerebellar nuclei synapse (reviewed in [89, 76]). At variance from classical LTD, some forms of LTP are purely presynaptic, for others there is evidence for a bidirectional postsynaptic switch [163, 167]. For all of these, the experimental results are now sufficiently clear to formulate appropriate learning rules and gating processes (e.g., see [166, 29, 52, 178, 75]. Thus, the cerebellar network is plastic in a more extended sense than originally envisaged. The functional meaning of this extended plasticity in computational terms remains largely to be assessed.

The plasticity issue requires further comments. First of all, that just because a synapse can be shown to be plastic, does not necessarily mean that it is involved in "learning" in the classical sense. It is likely that at some level all synapses in the brain are plastic, the question is for what functional purpose. For example, the classical parallel fiber−Purkinje cell LTD is Hebbian and supervised in nature, while the aforementioned mossy fiber−granule cell LTP and LTD are Hebbian but unsupervised, with fundamentally different impact on learning and behavior. In fact, as far as we can understand, plasticity in the granular layer could tune the response timing of specific granule cells and therefore the activation patterns of Purkinje cells, opening questions about the meaning of "motor learning". Secondly, some forms of LTD appear to be trans-synaptic. That makes cerebellar learning, explicitly not-Hebbian. The apparent fact that active parallel fiber synapses can influence the weights of inactive parallel fiber synapses is a fundamental problem for traditional theories of cerebellar Purkinje cell learning [76].

4.2.5. *Cerebellar synchrony, oscillations and resonance*

The first hints that the cerebellum might generate coordinated activities was raised by the discovery of gap junctions (the molecular correlate of the electrical synapses) in the inferior olive between olivary neurons and in the molecular layer between stellate cells [178, 119]. More recently, gap junctions have been observed in the granular layer between Golgi cells [58, 188]. It was then observed that, as well as other major systems of the brain (like the thalamo-cortical system), also the olivo-cerebellar system can generate rhythmic activities (reviewed in [35, 47]). In addition, intrinsic neuronal properties can contribute to generate oscillations: the inferior olivary neurons can generate theta-frequency oscillations, and recently a similar property has been found in Golgi cells [55, 66].

Low-frequency oscillations are fundamental for several neurophysiological processes, including sensory motor control, the formation of memories and sleep (for review see [23]. Sensory motor control is based on 6−9 Hz oscillations [74] spreading through a cerebro-cerebellar loop involving cerebral cortical areas (prefrontal cortex, PFC; premotor cortex, PMC; primary sensory motor cortex, S1-M1; posterior parietal cortex, PPC), cerebellum, thalamus and back to the cerebral cortex [161]. The fundamental operations controlled by cerebro-cerebellar loops are explained through the "timing hypothesis" (the temporal goal is a requisite component of the task representation [182]) and the "sensory prediction" hypothesis (match between the predicted and actual sensory outcome of motor commands [59]), [182, 95, 94]. The proposed functions of the cerebro-cerebellar loop include motor sequence generation, sensory motor control, switching of attention and decision making. Some circuit elements of the cerebro-cerebellar loop can intrinsically generate and sustain the rhythm while others are probably entrained by circuit activity. These two mechanisms, entraining and being entrained, are probably not disjoined because large-scale brain oscillations are collective processes, in which coalitions of neurons transiently reinforce their reciprocal interaction. Voluntary movement causes oscillatory activity in the prefrontal areas, which then propagates to the PMC, S1-M1, PPC and is then relayed to the cerebellum (through pontine nuclei). The cerebellum may therefore initially be entrained and then participate to reinforce theta-band oscillations in the cerebro-cerebellar loop.

Both the granular and molecular layer can be entrained into theta-frequency cycles driven by the cerebral cortex [34, 154, 124]. The granular layer spike patterns, once recognized by Purkinje cells, could set up theta-frequency oscillations in specific subsection of the inferior olive−Purkinje cell−deep cerebellar nuclei system (see above). Due to climbing fiber branching, this activity would affect specific groups of Purkinje cells located along the sagittal axis. The parallel fibers (which can reliably transmit at low-frequency, see above), could drive into the theta-frequency Purkinje cell beams located along the transverse axis. The final effect would be a positive interference of theta-frequency activity in Purkinje cells that lie at the intersection between the transverse (parallel fiber-driven) and sagittal (climbing

fiber-driven) groups. This mechanism could provide the necessary coherence for multiple inputs occurring in different regions of the cerebellum, extending the concepts of congruence of climbing and mossy fiber signals [107, 21].

5. Hypotheses and Open Issues for Cerebellar Functioning

The recent findings on cerebellar neurons and circuits reported above [39] suggest to revisit concepts on cerebellar network functioning in view of the spiking nature of neuronal outputs, of the specific dynamic processing that neurons and synapses impose to input signals, and of the intricate interconnectivity within the network. For simplicity of description, cerebellar operations can be divided into the following three steps:

(1) Spatio-temporal reconfiguration in the granular layer
This sub-circuit provides the *gain and phase regulation* required to reconfigure the input signals, eventually emitting spike patterns appropriate to control molecular layer interneuron and Purkinje cell activity [37]. Signals coming as bursts along the mossy fibers are reconverted into bursts and several processes control the granular layer output pattern (delay, duration, frequency, regularity), including synaptic plasticity, tonic and phasic inhibition and glomerular crosstalk. Feed-forward inhibition enforces the *time-window* mechanism and cause the emission of patterns consisting of short spike bursts (1−3 spikes) at high frequency maintaining high temporal precision (ms range). Presynaptic expression of long-term synaptic plasticity at specific mossy fibers−granule cell synapses and intrinsic excitability regulation in granule cells provide the basis for storing memory in the circuit (*learning*). Eventually, the architectural arrangement of circuit elements would allow to combine and sort different inputs and to distribute the output along many more lines (*expansion recoding*) with differential delays and gain determined through long-term synaptic plasticity. In this manner, the granular layer analyzes the signals and subdivides them into their multiple components (*adaptable filtering*) (Figs. 3 and 4). This mechanism can generate the *spatio-temporal transformation* required for ordering signal sequences in a complex input space. These include commands sequences emitted by the cerebral cortex or coming from different sensory systems (*timing*) and ensembles of cerebro-cortical commands and feedback sensory signals during voluntary movements (*sensory prediction*). This mechanisms operate on the 1−100-ms scale, and could account for learning elementary associative behaviors like eye-blink conditioning and conditioned responses in general. On a longer time scale, synchronization processes are needed. These can be provided by *low-frequency oscillations*, which can set the coherent temporal framework on the 100-ms scale for the synchronization of complex data-sets and repetition of activity cycles. In the vestibulo-cerebellum, the additional presence of UBCs could allow for further *temporal storage* required for implementing slow VOR reactions.

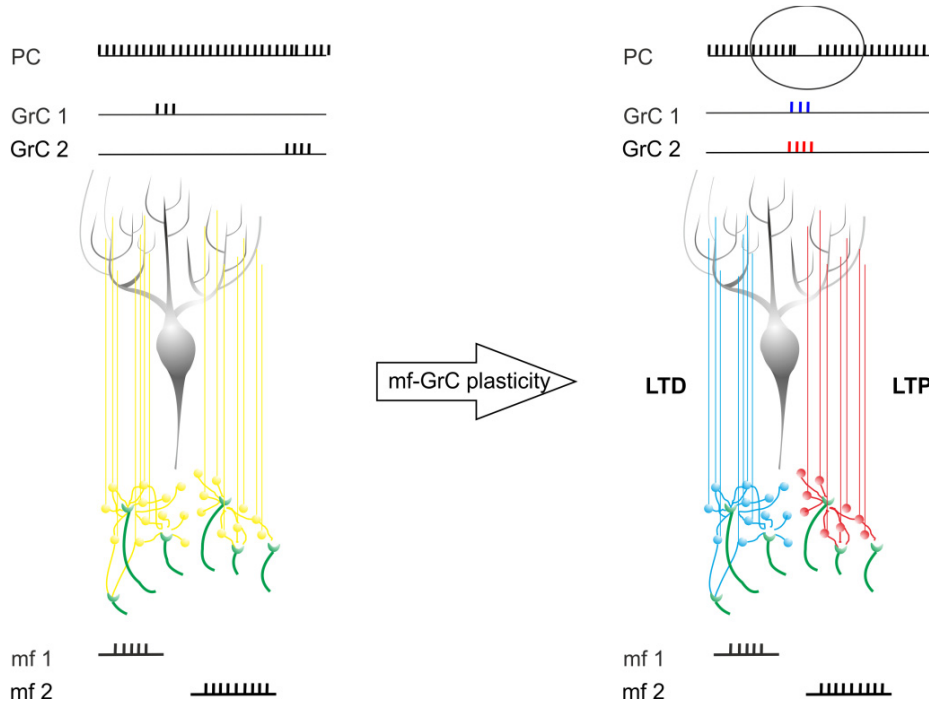

Fig. 4. Hypothesis on spatio-temporal reconfiguration in the cerebellar network. The figure illustrates how LTP and LTD could regulate coincidence detection in the cerebellum. The first of two mossy fiber signals is delayed by LTD, the second is anticipated by LTP (see [37]). When both signals are aligned, their coincidence is detected as a large depolarization in Purkinje cells and molecular layer interneurons generating a burst-pause response [179].

(2) Signal synthesis in the molecular layer and deep cerebellar nuclei

The molecular layer elaborates the patterns generated by the granular layer. These patterns arrive along *vertical lines* organized in *center-surround*, so that activation of Purkinje cells and molecular layer interneurons laying above a specific granule cells *cluster* is privileged [17, 152, 18, 151]. Transmission along this line is almost instantaneous (<1 ms), consistent with the fact that delay regulation occurs in the granular layer [56]. Parallel fibers may not be important either to activate specific Purkinje cells or to generate remarkable delays, but rather to transmit low-frequency patterns and to set the background discharge of Purkinje cells. The Purkinje cells would operate as oscillators, whose frequency can be almost instantaneously increased or reduced by the contribution of their numerous inputs along the ascending brand and parallel fibers. The molecular layer interneurons can generate a pause just after Purkinje cells have discharged, accentuating the burst-pause pattern and maintaining the precision of response into the ms range (*timing*). By collecting information from as many as 200,000 granule cells, the Purkinje cells are well suited to operate the *synthesis* of the multidimensional granular layer transformations. Plasticity at the mossy fiber−Purkinje cell synapses and at molecular layer interneuron−Purkinje cell synapses can store the patterns detected

from the granular layer generating a more stable, reach and redundant representation of the input space. Inputs from the inferior olive can provide further synchronizing signals at low frequency, potentially integrating with the low-frequency oscillations conveyed from the granular layer, and could also favor LTD on parallel fibers activated in close time synchrony (Fig. 3). The UP/DOWN states could extend timing regulation in Purkinje cells over the second range.

Eventually, deep cerebellar nuclei neurons need to be able to perform a secondary synthesis by sampling several Purkinje cell contributions as well as inputs from the mossy fibers [13]. This operation needs also to occur with ms precision to account for the final precision of the cerebellar computation and of motor behavior as a whole.

(3) Modularity and synchronization in the deep cerebellar nuclei/Purkinje cell/inferior olive loop

The cerebellum is organized in a manner that allows the operation of multiple modules with partial interdependence. In such modules, the mossy fibers and the Golgi cells distribute their ramifications to the granule cells and the climbing fiber activate multiple Purkinje cells on the sagittal axis. The activity in the granular layer is organized in clusters, which provide a preliminary selection of active neuronal assemblies. Conversely, parallel fibers travel along the transverse axis allowing to merge the mossy fiber and climbing fiber pathways at the multiple intersections of the two afferent fiber systems. This organization could allow to organize the numerous granule cell clusters and Purkinje cells activated by the mossy fiber pathway into functional assemblies provided by climbing fibers following activity generated in the inferior olive. The inferior olive−Purkinje cell-deep cerebellar nuclei loop could also be able to generate low-frequency sequences based on the migrating depolarizing waves observed in the inferior olive and on the feedback control exerted through inhibitory deep cerebellar nuclei−inferior olive connections [97]. The synchronization of low-frequency activity in the deep cerebellar nuclei /inferior olive/Purkinje cell loop with the mossy fiber input may occur at the intersection of granular layer clusters and climbing fiber domains as well as though the influence of the climbing fibers on the granular layer (Fig. 3).

5.1. *Learning and timing: An integrated hypothesis on cerebellar mechanisms*

Learning seems to occur at multiple critical points in the cerebellar network [76, 163, 49]. Distributed learning would allow a maximization of storing capabilities and may have different meaning in different subcircuits. In the granular layer, LTP and LTD are translated into signal timing and determine a spatial reconfiguration of activity (Fig. 4). In Purkinje cells, LTP and LTD could have the role of revealing the appropriate coincidence detection of impulses coming from the parallel fibers and climbing fibers. In the deep cerebellar nuclei, LTP and LTD could have the role of revealing the appropriate coincidence detection of impulses coming from the mossy fibers and the Purkinje cells. Plasticity in the inhibitory loops provided by the Golgi

cells and molecular layer interneuron may be homeostatic, counterbalancing the modifications of strength along the main mossy fiber−granule cell−Purkinje cell axis. In all cases, various mechanisms seem suited for regulating different aspect of learning and memory and to translate it into circuit operations. However, eventually plasticity at multiple sites could have a reflection on gain and timing, so that distinguishing a specific role of plasticity for each type of synapse may be quite hard.

Since the cerebellum is thought to learn how to order input sequences (e.g., activation of muscles in a complex movement) and how to determine the proper matching between inputs of different origin (e.g., motor commands and sensory feedback), long-term synaptic plasticity could be primarily involved in setting the appropriate reaction times of the different elements in the network (see Figs. 3 and 4) [37, 38, 48]. Let suppose that signals come with different delay but need to be synchronized in order to allow their simultaneous processing. This case is relevant indeed, since the Purkinje cells have a limited integrative time window (about 10 ms) that is dictated by their membrane time constant and would therefore process two inputs as coincidental only if they fall within the same time window. This time window matches the spontaneous firing of the Purkinje cell: with a basal rate of 50−100 Hz, spike displacement would be meaningful on the scale of a few milliseconds. Now let assume that signals are channeled through two granule cell clusters (Fig. 4). If LTD delays the response of the first granule cell cluster and LTP anticipates the response of the second, signals coming from the two clusters would arrive simultaneously on the receiving Purkinje cells. In order to better exploit this mechanism, the granule cell clusters need to be aligned with the same Purkinje cells (related clusters lay indeed in close vicinity). The Purkinje cells should therefore be able to perform the comparison of the two signals through coincidence detection of the two stimuli [22]. Important to say, the perceptron operation can exploit a second alignment provided by feedforward inhibition exerted by molecular layer interneurons [85].

In this way, a motor command could be aligned with its related sensory feedback arriving tens of milliseconds later. Or a conditioned and unconditioned stimulus could be associated over a 100-ms scale. Or, by an inverse mechanisms of decoupling, a global motor command (e.g., a reaching movement of the arm involving well-timed sequences of shoulder, elbow, wrist and fingers extensions) could be decomposed into an appropriate timed sequence of commands for the different muscles involved. Operations of logical association of exclusion could further ordinate cluster activity [121]. By regulating the parallel fiber synaptic strength appropriately, the Purkinje cell would then set the contribution of the different clusters to the combined signal. In response to the simultaneous activation through the two clusters, the Purkinje cells could eventually be able to generate a burst-pause response. One should then imagine to reiterate the process over many clusters and over many Purkinje cells. Eventually, the convergence of these many Purkinje cell signals on the deep cerebellar nuclei neurons would impart the correction to the mossy fiber inputs that these latter neurons receive.

Clearly, in order to have this mechanism working properly one needs to imagine local learning rules with the following properties: (1) The active cluster in the granular layer should influence each other, thus generating LTD and LTP in specific orders, (2) learning should be regulated by neuromodulators relating it to the attentional and global state of the subject, (3) plasticity should be reversible in case of changes in the motor strategy (e.g., inversion of a reflex) or osteo-muscular conditions (e.g., a change in load or an injury), (4) plasticity should be consolidated (e.g., through gene expression and protein synthesis) to ensure its long endurance, (5) mechanisms of saving should be enabled to recover previous memories after reconfiguration, (6) learning should be coordinated by low-frequency oscillations under the guidance of climbing fibers and the control of cortico- cerebellar dynamics. The identification of the corresponding cellular mechanisms is a challenge for future research.

The mechanism could be exploited in several contexts. In the eye-blink conditioning reflex, the conditioned and unconditioned stimuli have to be precisely associated through learning with precision of few milliseconds, implying mechanisms compatible with those considered here in the granular and molecular layer. In programming a saccade, the eye moves at high constant speed in a ballistic manner and the control of its end-point corresponds to the time required to reach it with a precision on millisecond scale. Again the present mechanisms could guarantee the association of the sensory and motor cues through memories appropriately preprogramming the execution times. In the vestibulo-ocular reflex, plasticity could account for adaptation of phase and gain of the reflex, and the longer execution times could require protracted excitation along UBC chains.

This timing/learning mechanisms could provide the substrate for coordinated signal processing in the 100-ms range with precision on the millisecond scale [46]. Longer sequences could be ordered on the basis of theta cycles, which repeat every about 100 ms (Fig. 3). This is indeed the dominant activity initiated in the cerebral cortex when a motor command is generated and into which the cerebellum is entrained [74, 161, 162]. In the Purkinje and deep cerebellar nuclei cells, climbing fibers could deliver signals correlating learning with the theta-frequency cycle.

6. Conclusions and Future Directions

This revision on functional mechanisms of the cerebellum shows that original postulates need to be profoundly revisited in view of the recent acquisitions of cellular and circuit neurophysiology and of computational modeling.

As far as the general function of the cerebellum is concerned, in addition to the well established role in sensory motor control, a role in cognition and emotion is also receiving support. Available observations suggest that this is not just used for improving motor control but also to generate a broad-range control of cerebral functioning. The proposal that the cerebellum makes use of a standard circuit structure to control multiple aspects of brain activity remains to be demonstrated.

The granular layer emerges with novel functions and with much more relevant and complex properties than previously thought for spatio-temporal reconfiguration of the inputs. The role and function of Purkinje cells and deep cerebellar nuclei cells in signal processing is under re-evaluation and crucial issues remain to be solved about the functional mechanisms of these neurons and their plastic modifications. Moreover, circuit architecture is not yet fully defined with open questions regarding the functional connectivity between the inferior olive system and the granular layer, between mossy fibers and Purkinje cell and between Purkinje cell and deep cerebellar nuclei. Beside this, it is not yet clear how the cerebellum forms its specific connectivity during ontogenesis [155], which presumably implies both programmed mechanisms and structural plasticity.

If understanding signal coding and morpho-functional connectivity still reveals unknown aspects, understanding the role of plasticity seems even harder. A critical and yet unresolved issue is not just about how the learning rules operate but also about how learning is controlled. Learning cannot occur indiscriminately but needs to be gated to allow its deposition at specific synapses, to prevent destructive interference with previously acquired memories, and to provide a simple and reliable mechanism to store information about multiple tasks. The role of teacher and instructor attributed to the climbing fibers by theory seems far too simple to cope with the complexity of synaptic processes revealed in the cerebellum and does not answer to the question of where motor errors are detected. A related paradox is that of "temporal credit assignment", since the climbing fibers, which are supposed to convey the motor error, generate the calcium spike required for LTD before parallel fibers, which relay the signals to be learned. If the cerebellum has to detect the motor errors and process them in coincidence with the motor commands, it should therefore embed appropriate mechanisms to do so rather than be taught by an external entity. This external teacher has in fact never been identified but may not be the inferior olive, which rather works as a highly synchronized and specialized clock. It is therefore suggested that the learning rules and their control mechanisms will have to be identified within the cerebellar network itself (e.g., through mechanisms like that proposed in Figs. 3 and 4).

Beside these unresolved aspects, the cerebellar circuit appears well suited to regulate timing in the millisecond range, to order complex multidimensional sequences on the theta-band, to compare different sets of inputs and to regulate its internal dynamics on the basis of learned synaptic modifications. In its essence, the historical contrast between *learning* and *timing* could be solved by considering that synaptic plasticity is the substrate for tuning the timing mechanisms of the cerebellar circuit and that oscillations and resonance regulate plasticity ("*plasticity is timing*"). These mechanisms can in turn implement a general algorithm allowing to reconfigure incoming patterns in the huge multidimensional space of the mossy fiber input. This algorithm, by operating inside different brain loops, could determine the various functional and pathological consequences of cerebellar activity. Realistic modeling can provide a critical step toward the reconstruction and investigation of

these network properties (e.g., see [166, 176, 127, 107, 148, 101]). Casting these concepts into a well-defined theoretical framework (which, like the adaptive filter theory, may be able to incorporate learning rules and cell dynamics [51]), could provide new clues on cerebellar circuit functioning reconnecting biology to general theories of signal processing and eventually explaining how the cerebellum is actually operating.

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FUNCTIONAL RECOVERY FOLLOWING MOTOR CORTEX LESIONS IN NON-HUMAN PRIMATES: EXPERIMENTAL IMPLICATIONS FOR HUMAN STROKE PATIENTS

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This review discusses selected classical works and contemporary research on recovery of contralesional fine hand motor function following lesions to motor areas of the cerebral cortex in non-human primates. Findings from both the classical literature and contemporary studies show that lesions of cortical motor areas induce paresis initially, but are followed by remarkable recovery of fine hand/digit motor function that depends on lesion size and post-lesion training. Indeed, in recent work where considerable quantification of fine digit function associated with grasping and manipulating small objects has been observed, very favorable recovery is possible with minimal forced use of the contralesional limb. Studies of the mechanisms underlying recovery have shown that following small lesions of the digit areas of primary motor cortex (M1), there is expansion of the digit motor representations into areas of M1 that did not produce digit movements prior to the lesion. However, after larger lesions involving the elbow, wrist and digit areas of M1, no such expansion of the motor representation was observed, suggesting that recovery was due to other cortical or subcortical areas taking over control of hand/digit movements. Recently, we showed that one possible mechanism of recovery after lesion to the arm areas of M1 and lateral premotor cortex is enhancement of corticospinal projections from the medially located supplementary motor area (M2) to spinal cord laminae containing neurons which have lost substantial input from the lateral motor areas and play a critical role in reaching and digit movements. Because human stroke and brain injury patients show variable, and usually poorer, recovery of hand motor function than that of nonhuman primates after motor cortex damage, we conclude with

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a discussion of implications of this work for further experimentation to improve recovery of hand function in human stroke patients.

Keywords: Motor cortex; lesion; hand; grasp; manipulation.

1. Introduction

Our goal is to provide an overview of selected classical works that, largely through the use of surgical ablation techniques, have provided foundational support for our contemporary understanding of the neuroanatomical and functional characteristics of the motor cortex. These classical works, coupled with contemporary studies, provide an excellent forum to discuss their implications for the clinical features and expectations of stroke recovery. To accomplish our goal, we have limited the scope of this review primarily to the effects of long-term motor cortex lesions in nonhuman primates on contralateral upper limb function, in particular for reaching and grasping objects, including the use of precision grip of small objects. It is not surprising that the study of upper limb recovery has attracted so much attention over the years, considering the common neurological occurrence of paresis and the difficulty many patients have regaining dexterous movements. In accord with others, it is our contention that continued study of the behavioral, neuroanatomical, neuronal, and biochemical consequences of damage to motor cortex or its descending projections that affects upper limb reaching function will help us better translate between basic science advances and their clinical application [17, 110].

In this review, we will reference work on the motor cortex and the areas immediately adjacent. Our use of the term "motor cortex" will exclusively refer to the primary motor cortex (M1) located in the precentral gyrus of man and higher-order non-human primates. Other motor areas referred to throughout this discussion will include the lateral premotor cortex (LPMC), located just anterior to precentral sulcus in man and anterior to M1 in macaques (dorsal portion of LPMC being dorsal to the superior limb of the arcuate sulcus and ventral portion being caudal to the inferior limb), and the supplementary motor area (M2), located medially to LPMC in man and macaques (Fig. 1). Given that the reciprocal sensory information terminates immediately adjacent to the primary motor area in the postcentral gyrus, we will also discuss the basic implications of the primary sensory (S1) area (Fig. 1).

2. Localization and Mapping of Motor Cortex

Early investigations into recovery after motor cortex lesions began with reports that damage to the precentral gyrus caused no sensory loss, and resultant movement problems varied in intensity and duration (e.g., [30]). This work originated in the classical era of functional localization, which was a highly controversial topic in the early to middle parts of the 19th century. During this time period, some scientists, led in part by the dominant influence of Pierre Flourens, held that the cerebral cortex was the seat of intelligence and sensation, while motor function was

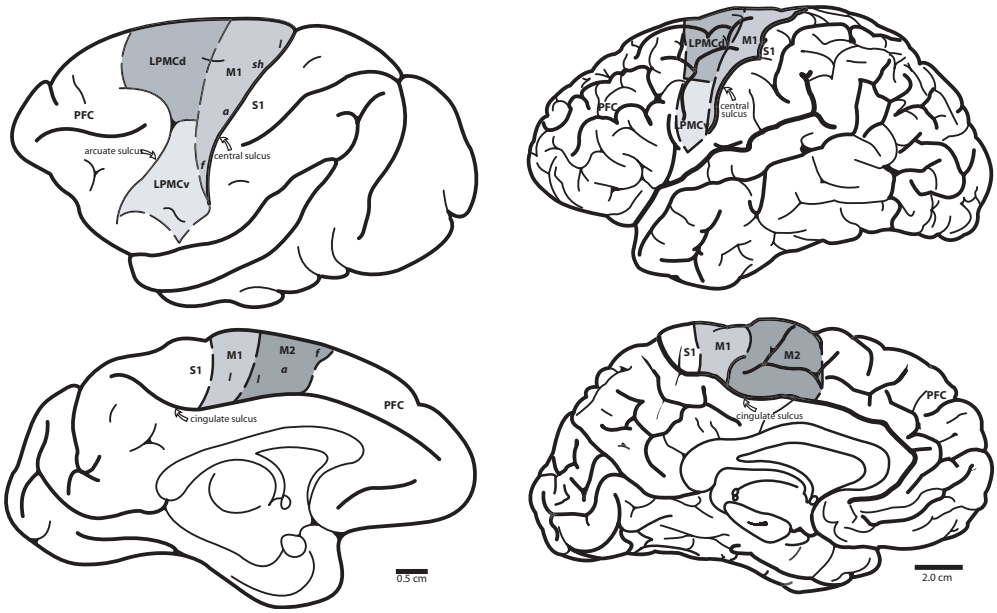

Fig. 1. Drawings of lateral and medial (sagittal) views of monkey (*Macaca mulatta*) on the left side and human cerebral cortex on the right side showing major motor and sensory areas and prefrontal cortex. Abbreviations: M1: primary motor area, LPMCd: dorsal portion of lateral premotor cortex, LPMCv: ventral portion of lateral premotor cortex, M2: supplementary motor area, PFC: prefrontal cortex, SI: primary somatosensory area, f: face, a: arm, sh: shoulder, l: leg.

subserved by subcortical structures including the cerebellum ([34] as cited by [16]). Such views were based on experimental studies conducted by Flourens in "lower animals" such as dogs, frogs, and birds. In retrospect, it is thought that the lower functional capacity of these animals, and the probability that these experiments were conducted in young animals, may have contributed to his inability to localize motor function at the cortical level [33]. However, in 1870, Fritsch and Hitzig identified distinctive sites on the cortical surface of the dog brain, which, following the direct application of low levels of electrical current, elicited contralateral movements in isolated body parts including the regions of forepaw, hind paw and face ([35] as cited by [112]). This ground-breaking publication provided key support for not only the controversial idea of cortical localization, but also the long awaited experimental documentation for a cortical role in motor function. Subsequent studies in higher animals (e.g., monkeys), using more refined stimulation of the brain surface, in conjunction with ablation methods, demonstrated more detailed evidence of localization of motor function in the frontal lobes and major sensory functions in the parietal, occipital and temporal lobes (Fig. 2) [30, 45]. Indeed, when parts of the gyri spanning the Rolandic fissure (central sulcus) were lesioned by electrocautery, it was possible to observe in monkeys motor deficits to individual limbs on one side of the body (hemiplegia) (Fig. 3). These motor deficits were very similar to those observed in humans after stroke or traumatic brain injury that affected well-defined parts of the brain as confirmed post-mortem [30]. Recovery

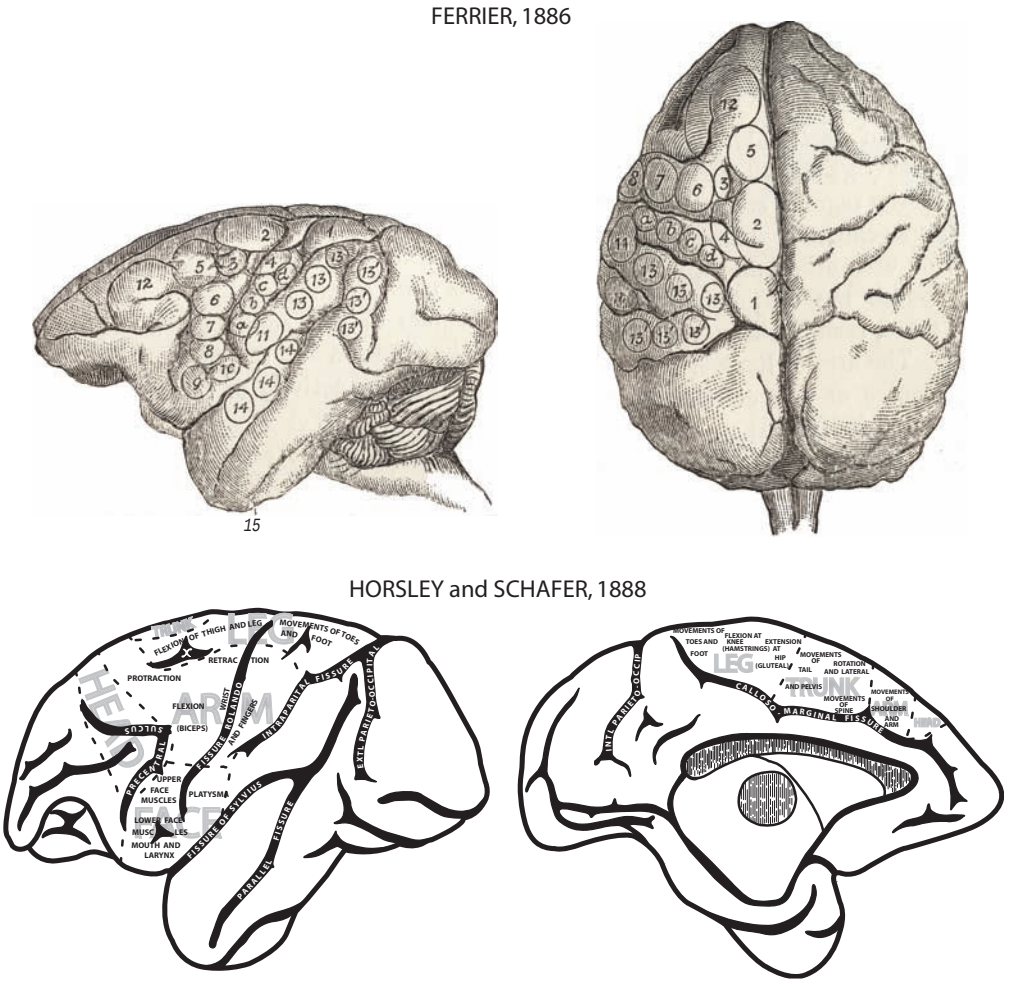

Fig. 2. Montage depicting motor organization of the cerebral cortex determined by the application of electrophysiologic stimulation of the cortical surface in monkeys. Top: Lateral (left) and dorsal (right) views of the cortex with distinct movement representations outlined by irregular circles with numbers published by the British neurologist David Ferrier [29]. The sites that evoked movements in the upper limb are numbered 4 ("retraction with abduction of the opposite arm"), 5 ("extension forward of the opposite arm and hand"), a, b, c, d ("individual and combined movements of the fingers and wrist" for prehension of the opposite hand), 6 (supination and flexion of the forearm). Bottom: Lateral (left) and medial (right) views of the cortex with movement representations published by Horsley and Schafer [45]. This map provides one of the most comprehensive representations of the motor cortex published in the 1800s. Of notable significance was the early recognition of head, arm, trunk, and leg representations on the lateral surface of the hemisphere as well as the medial surface.

from such experimental lesions was typically poor, with at least weakness and paresis persisting for long periods. Similarly, surgical removal of portions of cortex that produced muscle contractions when stimulated led to long duration paralysis of the limbs on the opposite side of the body, although some recovery of trunk muscles was observed (Fig. 3) [45]. In many cases, it appears from the descriptions and published figures that these lesions spanned the central sulcus, thereby affecting

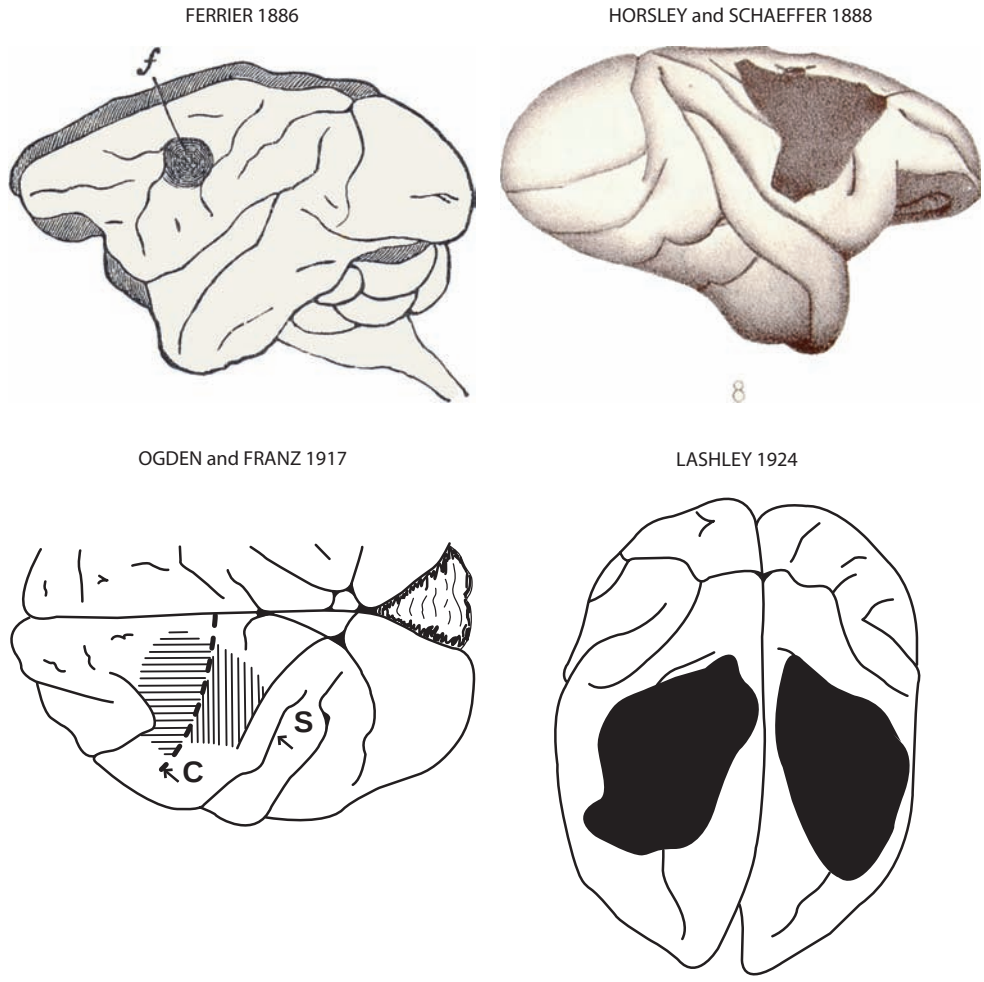

Fig. 3. Montage depicting the precentral motor lesion site in monkeys in the classic studies of Ferrier [29], Horsley and Schaffer [45], Ogden and Franz [79] and Lashley [52] (Fig. 1, American Medical Association, Archives of Neurology and Psychiatry, reproduced with permission). In the Ogden and Franz map, the horizontal lines indicate the first surgical ablation which involved the excitable precentral motor cortex. The vertical hatching over S1 indicates an apparent abnormality of that area. In the other maps, the frontal motor lesion site is represented by the blackened region.

both sensory and motor areas and extended into adjacent premotor cortex (Fig. 3). Moreover, it is also likely that the lesion may have included the underlying subcortical white matter of the corona radiata.

3. Injury to the Motor Cortex and Recovery

These very early investigations were followed by studies of motor recovery in the early 20th century following carefully performed surgical lesions to specific areas of M1 in nonhuman primates including lemurs, macaque monkeys and great apes [40, 59, 70] (see [112] for a review). In general, these studies confirmed previous work

indicating initial flaccid paralysis of the contralesional limb(s); but in contrast to previous work, remarkable recovery of limb function was observed during the postlesion period of two through eight weeks. For example, it was reported that "full recovery" was possible after removing the arm area of M1 (identified using electrical stimulation with low currents) in great apes (e.g., [39, 59]). These lesions were typically quite large, with depths of 6–8 mm and probably included some damage to the subcortical white matter of the corona radiata. In a series of experiments, Graham Brown and Sherrington [39] investigated the results of motor cortex damage in a chimpanzee that received a lesion of the arm area of left motor cortex on July 27, 1912 and had apparently recovered full function of the right arm by December, 1912. A second surgery was then performed where the arm area of right motor cortex was lesioned. This had no effect on right arm motor function and thus, was unlikely to have been responsible for its recovery. Also notable was that the left arm recovered function more quickly than the right arm had recovered after the first surgery. Next, in a third surgery, the arm area of the right postcentral gyrus was lesioned on February 5, 1913 and, "within 90 minutes of coming out of narcosis the ape gave the left hand at command" (presumably to shake the experimenter's hand) and "None of the movements of the left arm were absolutely lost, but there was a considerable weakness in some of them." Within a month (before March 15, 1913 when this note was published),

> *. . .the movements of the arm gradually improved and became stronger. He now sometimes feeds himself, for instance, with the left hand alone. He often transfers a banana from one hand to the other and it has been observed on several occasions that he can do this accurately without looking at either hand.*

Years later, Leyton and Sherrington [59] described another chimpanzee that recovered from an isolated ablation lesion to the distal arm area (thumb, fingers, wrist, and elbow representation) of left motor cortex to the point of being able to use precision grip to pick up small food objects with the contralesional hand having no postlesion "therapy" or training. However, some loss of independent movement of the index and strength of thumb grip apparently remained. After this partial recovery, and during a second surgical exposure, stimulation of the left hemisphere yielded no response from the lesion site or the intact postcentral cortex. Collectively, the findings from these two classic reports led to the conclusion that recovery of hand movement in higher-order primates could not be attributed to taking over of function by the motor cortex in the opposite hemisphere or by the postcentral gyrus (S1) of the lesioned hemisphere.

Another important observation of Leyton and Sherrington [59], which demonstrated that they were unable to evoke distal upper limb movements by stimulating the undamaged portion of M1 from the first lesion, warrants further discussion. Specifically, during the second surgery, they stimulated noninvolved (spared) cortex surrounding the previous M1 lesion in an attempt to elicit distal upper limb

movements. Stimulation of intact cortex dorsal to the lesion site evoked shoulder movements and stimulation of cortex ventral to the lesion-evoked face movements. However, no peripheral movements were observed in the hand and wrist and only questionably at the elbow. They concluded from this observation that portions of motor cortex that normally controlled face, trunk and lower limb movements of M1 did not have the capacity to take over the function of the damaged portion of the M1 wrist and hand representation. In a corollary component of their study, Leyton and Sherrington [59] also investigated the potential neuroanatomical consequences of the cortical lesions from histologically processed tissue sections through the medulla oblongata and spinal cord. Using the Marchi technique, microscopic observations revealed that the cortical lesion produced substantial myelin degeneration of the descending cortical projection in the pyramidal tract, both at the level of the medullary pyramids (on the side ipsilateral to the cortical lesion) as well as in the lateral and ventral corticospinal tracts (CSTs) in the cervical enlargement (contralateral to the lesion). In contrast, minimal tissue deterioration was noted in thoracic cord spinal levels and none at levels through the lumbar enlargement. These findings provided strong neuroanatomical evidence that the lesion was primarily restricted to the cortical neuron field projecting to spinal cord levels controlling the upper limb.

Complete recovery from large lesions that affected the entire "stimulable cortex" (M1 + dorsal part of LPMC) of one (left) hemisphere, were also demonstrated in early work (Fig. 3) [79]. Immediately after the lesion, there was flaccid paralysis of the contralesional limbs as reported in previous studies. However, constraint of the ipsilesional upper limb and daily movement therapy of the contralesional upper and lower limb (similar to constraint-induced movement therapy presently used for hemiplegic stroke patients — [104, 113]) produced what Ogden and Franz considered full recovery of upper and lower limb function, as well as body posture. Interestingly, much of this recovery occurred over the first two weeks following the lesion and appeared largely complete at three weeks postlesion as the monkey was able to "pick small objects from the floor and convey them to the mouth" [79]. Indeed, they described this monkey using the contralesional hand to catch a fly "that had alighted in the monkey's cage" about three months after the lesion. As they eloquently stated: "The coordination and quickness for the performance of this act will readily be appreciated." Unfortunately, they did not specifically state whether the animal recovered precision grasp between the thumb and index finger and it does not appear that they specifically tested for, or reliably measured this ability. Animals that did not receive constraint of the ipsilesional upper limb and therapy for the impaired limbs remained greatly impaired in movements of the contralesional hand and digits (and of the contralateral leg as well as postural impairments) for up to six months after the lesion (see experiments 2 and 3 of Ogden and Franz [79]). Based on their observations, and those of others, it was concluded that full recovery was possible even after extensive damage to the entire stimulable (motor) cortex.

Similarly, Lashley [52] observed in monkeys who learned a complex series of movements to open "problem boxes" containing food rewards, that after a surgically induced lesion of stimulable cortex followed by subsequent recovery from paresis, the animals could again perform the complex task two months after the lesion almost as well as before the lesion (Fig. 3). Interestingly, after training to learn the task exposure to the testing apparatus was prohibited two months before the lesion and two months after the lesion to address the issue of acquired motor skill retention. Although the lesions for this study were described as involving the "precentral gyrus", the mapped lesions, as determined from the accompanying figures, appeared to also include what is currently considered the premotor cortex as well as the caudal region of the prefrontal cortex — see Figs. 1–3 of [52]. Furthermore, examination of the coronal sections in these figures also indicates some minimal involvement of the adjacent parietal somatosensory cortex. Even with this apparent larger cortical lesion, it was concluded that complex motor habits acquired prior to an experimental lesion of precentral gyrus were fully retained after the lesion, although some clumsiness may affect performance. These findings were later confirmed in monkeys with smaller lesions confined to the precentral motor areas (M1 and LPMC) [43, 46]. It is also important to note that Lashley [52] cited previous work conducted by Rothmann in 1907 in which he "observed learning in a rhesus monkey in which one precentral gyrus had been extirpated and the pyramidal tract of the other had been sectioned in the cervical region" [92]. This observation demonstrated that monkeys could learn a new motor task following a precentral gyrus lesion and cervical disconnection of the corticospinal projection from the opposite hemisphere. From a clinical standpoint, these results were very encouraging in terms of implications for rehabilitation of hand function in humans after stroke. In particular, acquired brain lesions affecting the lateral cortical motor areas, while preserving other cortical structures and their subcortical projections, including the medial areas along the interhemispheric fissure, resulted in the potential for recovery without extensive retraining. Furthermore, this body of work suggested that favorable recovery was possible even if the lesion extended into premotor areas with extensive training that included constraint of the ipsilesional limb. However, these findings seem to have been largely forgotten until constraint-induced movement therapy (CIMT) for hemiplegia was reintroduced by Taub *et al.* some 70 years later [103], but was based on results of experiments inducing deafferentation of the upper limb by sectioning dorsal roots in macaques [51, 102] rather than on stroke or motor cortex injury experiments.

After recovery of the right side was considered complete in experiment 1 of Ogden and Franz [79], a subsequent similar lesion was made in the stimulable cortex (M1 + dorsal LPMC) in the right hemisphere of the same monkey (experiment 2 of Ogden and Franz [79]). Following this lesion, the animal did not receive constraint of the recovered right upper limb or any therapy to the left limbs other than normal movements performed in its cage, and in a large exercise room. Walking and jumping showed some recovery but the animal tended to fall toward the left side and

did not always reach the target of a jump, suggesting left lower limb weakness. However, the left upper limb showed very poor recovery such that during climbing:

> *. . . the right arm and hand are used for pulling and the left is apparently used only for support. When food is given, even though the food be close to the left hand, the animal always reaches for the food with the right. Unlike a normal monkey which grasps and holds food with both hands and feet, this animal uses only the right hand and right foot.*"

Considering movement impairment resulting from brain injury, insights into our current understanding of the underlying corticospinal projections and transcallosal connections were evident in these early works. If the arm area of M1 was lesioned, resultant deficits appeared in the contralateral upper limb and recovery of function was possible. After recovery, when a subsequent lesion to the arm area of M1 of the other hemisphere was made, this new lesion did not reinstate deficits in the hand contralateral to the first lesion. Moreover, movement recovery was quicker in the second limb [59]. Similarly, Ogden and Franz [79] observed that lesion of the entire stimulable cortex of the other hemisphere did not affect the ipsilesional recovered limb, but produced contralesional hemiparesis that did not fully recover unless therapy was provided that included constraint of the recovered limb. The lack of effect of the second lesion on the hand contralateral to the first lesion provides strong evidence that the intact contralesional motor cortex did not take over control of the hand affected by the first lesion through ipsilateral pyramidal pathways. Moreover, the finding that recovery of the hand contralateral to the second lesion was quicker than expected is consistent with current theories that lesion to one hemisphere allows the other hemisphere to exert a form of dominance through transcallosal inhibition (TCI) of the injured hemisphere. Damage in both hemispheres after the second lesion may reinstate more balanced TCI between the hemispheres, thereby allowing better control of movement of both limbs.

As mentioned previously, an important finding from the work of Leyton and Sherrington [79] was that after recovery from the initial M1 lesion, they were unable to evoke contralesional distal upper limb movements when they stimulated the undamaged portions of M1 that were left intact from the first surgery. It appeared then, that the undamaged face, shoulder, trunk, and leg areas of M1 had not taken over the function of the damaged portion of M1. These results are consistent with the findings of Ogden and Franz [79], who showed that recovery of hand function (and leg/trunk function) was possible even after complete destruction of the entire M1 (and dorsal LPMC). Indeed, the observation that recovery was still possible after such large lesions, albeit when a form of what is currently called constraint-induced therapy [105] is applied to rehabilitate the monkeys, provides strong evidence that a simple reorganization of undamaged parts of M1 and/or adjacent LPMC cannot fully explain recovery of upper (or lower) limb function. That is, at least in the case of damage involving the portion of M1 and LPMC controlling an entire limb. Thus, in nonhuman primates and possibly stroke patients, other spared

cortical or subcortical areas may be capable of taking over some of the functions of the lateral motor cortices. This would be consistent with our recent report that M2 generates new connections (synaptic boutons) onto contralateral ventral horn neurons of the cervical enlargement following removal of the arm representation of M1 and LPMCd, and this plasticity correlates with recovery of dexterous hand movements [64]. The issue of rehabilitation training and its contribution to recovery of hand function after motor cortex damage will be discussed in more detail later.

4. Fine Motor Control Deficits Following Motor Cortex Injury

Following the classical work of the late 19th and early 20th centuries, further experimentation in apes and macaque monkeys provided evidence that lesions restricted to M1 produced flaccid paresis initially followed by substantial recovery and lasting deficits primarily in fine control of digit movements for manipulating small objects, especially in chimpanzees but also in macaques (Fig. 4) [37]. Lesions of premotor areas in addition to M1 produced more substantial disturbances such as spasticity and forced grasping initially, but these resolved after several weeks [37], which is consistent with the report of Lashley [52]. In contrast, Denny-Brown and Botterell later reported that lesions of area 4 produced flaccidity initially but was followed by "a spastic type of paralytic weakness" with heightened tendon reflexes whereas lesions of premotor areas produced "a mild plastic rigidity without loss of power of contraction and without increase in tendon reflexes" (Fig. 4) [23]. However, it was clear that even after large motor cortical lesions, the loss of use of an extremity was incomplete because given sufficient provocation such as fright or anger, a lesioned animal will effectively use the impaired extremity in climbing to escape or fighting back, even though under normal circumstances the extremity appears nonfunctional [23]. Such findings further support the ideas from Ogden and Franz [79] that under certain emotionally motivated conditions, an apparently severely impaired extremity can be retrained for complex motor acts, although it was thought that retraining fine control of the digits was not possible. These observations provided additional behavioral evidence suggesting other brain areas were indeed capable of taking over some functions of the lateral motor cortex. Although multiple cortical and subcortical neural networks are likely to be involved in this surprising restoration of movement, a potential contribution of the cingulate motor areas warrants consideration for several reasons. First, the rostral (M3) and caudal (M4) cingulate motor areas are well protected from lateral cortical injury as they form the cortex lining the lower bank and fundus of the cingulate sulcus. Second, they both receive substantial limbic cortical inputs [67, 69] which provide the cingulate motor cortices with a rich source of motivational and emotional influence that are essential requisites for the initiation and execution of exploratory movement involving the trunk and limbs. Finally, the cingulate motor cortices have substantial connections with the primary, lateral premotor and supplementary motor cortices

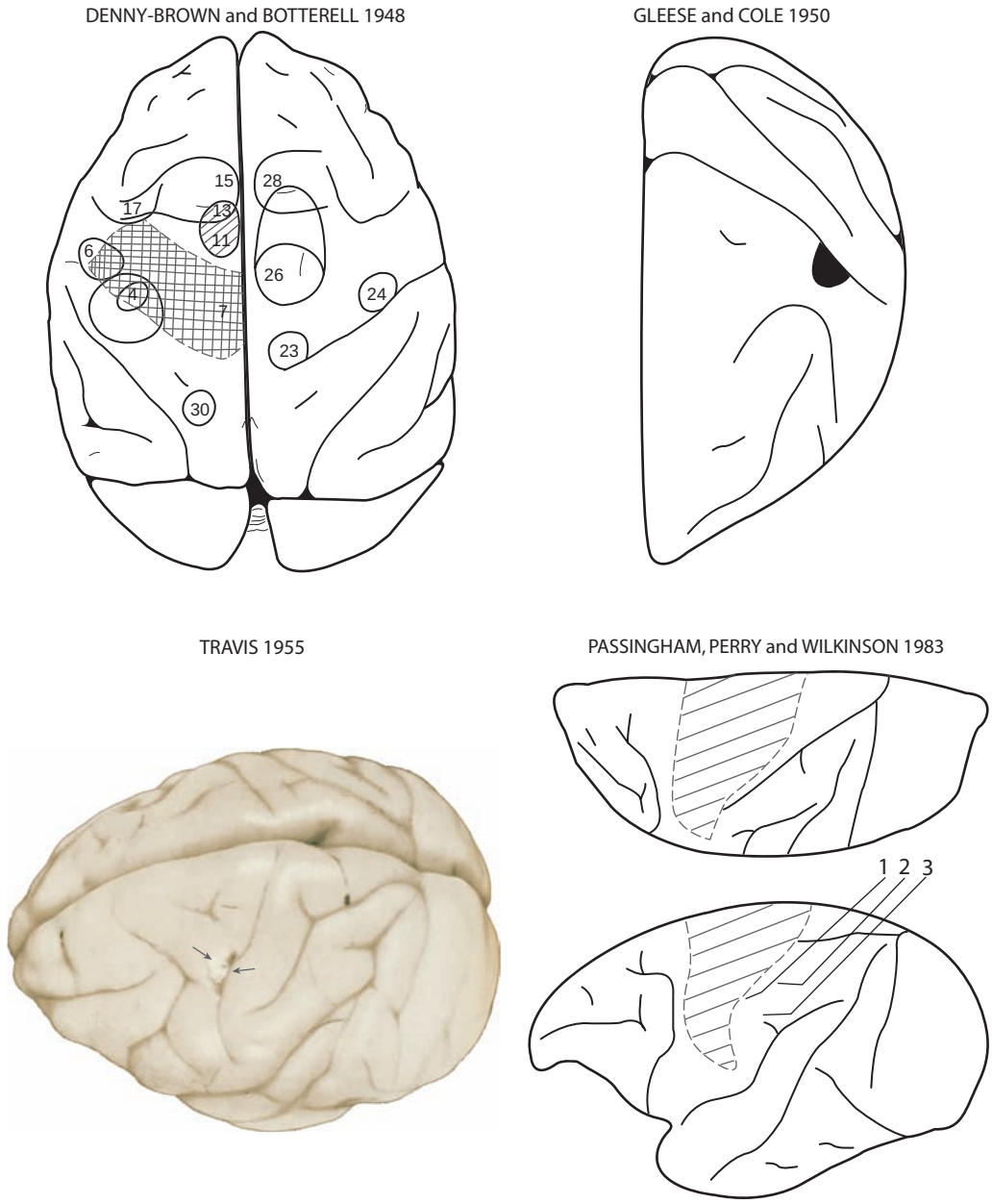

Fig. 4. Montage depicting the precentral motor lesion site in monkeys in the classic studies of Denny-Brown and Botterell ([23]; Fig. 6), Glees and Cole ([38]; Fig. 8, *Am Physiolog Soc*, *J Neurophysiol*, used with permission), Travis ([107]; Fig. 6, Oxford University Press, Brain, used with permission) and Passingham *et al.* ([84]; Fig. 1, Oxford University Press, Brain, used with permission). In the Denny-Brown map, the crosshatching indicates the surgical ablation which involved the arm and leg representations of the precentral motor cortex. In contrast to the typical large precentral lesion induced in most studies, the M1 lesion created in the Glees and Cole work (blackened area abutting the central sulcus), as well as the Travis [107] work (pericentral region indicated by the arrows), was small and discretely limited to the distal forelimb region of the arm representation. The lesion site in the Passingham figure is depicted by the diagonal lines and involved the face, arm, shoulder and leg representations of the precentral motor cortex.

and both M3 and M4 give rise to descending projections to many subcortical motor targets including the facial nucleus and spinal cord (for review, see [68]).

5. Neuroplasticity Following Motor Cortex Injury

Important experiments relevant to the effects of motor cortex lesions on development of reaching/grasping and differences in the effects of M1 and LPMC lesions as a function of age (infant vs. juvenile/adult monkeys and apes) were also carried out by Kennard in collaboration with Fulton during the 1930s and 1940s (Fig. 4) [47−50]. These classic experiments clearly showed that recovery was much more rapid in infant monkeys (7 days−3 months old) than in older animals (2−4 years). For example, complete lesions of M1 in very young infant macaques (7 days old) were associated with relatively little immediate effect and "complete recovery", including grasping and finger movements, by two months of age [47]. Older infants (42 days) also showed remarkable recovery even after removal of an entire hemisphere. For example, some recovery was noted within 24 hours and after a week, the infant could walk and climb. After a month, the infant could reach and grasp, albeit awkwardly. In contrast, adults with such a lesion showed much poorer recovery over the first postlesion month. Further research in which M1 and LPMC were removed bilaterally in a single operation or serially (i.e., left hemisphere and then right hemisphere 1.5−8 months later) again showed much better short-term motor recovery in infants than adults [50], but recovery over the long-term (up to two years) was studied only in infants as adults were all euthanized within 10−48 days of the lesion. Overall, these experiments showed that the infant brain was able to reorganize more rapidly than the adult brain to allow better recovery of motor function quite soon after the lesion(s). However, as discussed by Passingham *et al.* (see below), these experiments did not establish poorer long-term recovery in adults than in infants because the adults were not given up to two years to recover [84].

Experiments carried out in the 1950s strongly suggested that recovery of precision grip and fine digit control were possible following lesions of the entire arm or hand/digit areas of M1 (Fig. 4) [38, 107]. In particular, Travis [107] stated in reference to a rhesus monkey with a large lesion to the left precentral forelimb area: "After two weeks he picked up small pieces of food by apposition of the right thumb and index finger." Smaller lesions localized to the precentral hand/digit area (Fig. 4) were also made by Travis [108] and she reported that "after recovery from the anaesthetic the hand contralateral to the lesion was used almost as well as the normal hand." Glees and Cole [38] also reported, in contrast to earlier observations [40, 59], that stimulation of spared perilesional areas of M1 elicited hand/digit movements where prior to lesion, these movements were not evident. Thus, it appeared that the intact perilesional areas had taken over digit function of the damaged tissue areas. However, it is important to note that in the work of Leyton and Sherrington [59] during the first operation the entire elbow, wrist and digit areas

of M1 were excised whereas in the Glees and Cole work, only the thumb area was removed (Fig. 4).

More recent experimental work using intracortical microstimulation has complemented and expanded upon the findings of Glees and Cole. Specifically, Nudo *et al.* [74] elegantly demonstrated in squirrel monkeys that very small focal lesions affecting subsectors of M1 that elicit digit movements produces reorganization in spared subsectors to recover these M1 movement representations. Indeed, hand movement representations expanded into areas that formerly elicited shoulder/elbow movements, but only if rehabilitation in the form of training of skilled hand movements is provided after the lesion [77, 78]. Similarly, in macaque monkeys (*Macaca fascicularis*), it has also been shown that M1 hand area lesions in infant monkeys are associated with reorganization of perilesional cortex to innervate hand/digit muscles [93]. However, in the same species, a similar lesion induced in adult monkeys did not produce reorganization of motor cortex and, instead, was associated with reorganization of premotor cortex as short-term damage to this area reinstated the original deficit [62]. It is now well known based on observations from spike triggered averaging and single pulse intracortical microstimulation that single cortico-motoneuronal cells project to multiple muscles [10, 15, 31]. Furthermore, cortico-motoneuronal cells projecting to a given muscle controlling hand, wrist, elbow, and/or shoulder movements are distributed over large areas of M1 and overlap considerably in cat [1, 98] and monkey [25]. This expansive organization has also been postulated in humans based on transcranial magnetic stimulation observations [24]. Thus, muscle/movement map expansions in motor cortex may result after limited injury through altered connectivity within the cortex including the descending outputs ending directly in spinal motor areas, especially when use of the impaired limb is encouraged. However, others have reported in macaques that stimulation of the perilesional M1 after ibotenic acid lesions which damaged both M1 and S1 hand areas, did not produce visible movement of the "recovered" hand [62]. Notably, in this experiment, recovery was minimal, achieving only 30% of prelesion success rate on the task. It was also reported that reversible muscimol lesions to intact premotor areas reinstated impairment of the recovered hand, suggesting that these areas were responsible for the minimal recovery observed. Similarly, Nudo *et al.* have reported that following focal ischemic infarction affecting the distal forelimb (DFL) representation of M1 in squirrel monkeys, that initially produced severe deficits in reach/grasp motor abilities, was associated with enlargement of the DFL map in M2 [27]. Such findings are consistent with our recent report demonstrating that recovery of hand function following surgical removal of M1 and LPMC arm areas is associated with intraspinal sprouting and generation of new corticospinal connections from M2 into ventral horn neuron pools in C5-T1 segmental levels [64]. Thus, whether perilesional M1 or more distal sites in premotor cortex reorganize to assist in recovery may depend on lesion size, type (i.e., ischemic, chemical, surgical removal) and, possibly, location.

6. Measuring and Quantifying Movement and Skill

Also notable in the work of Glees and Cole [38] was that they developed a novel method to measure gripping strength between the thumb and index finger while pulling open a small "matchbox" drawer with a string to which they could attach different weights (see their Fig. 5). One rhesus monkey learned to perform the easiest version of the task (without weights) with both hands after the arm area of M1 in both hemispheres had both been lesioned by surgical removal (with no pre-lesion training on the task). Lesions were done serially, with the left hemisphere being lesioned first followed by lesion of the right hemisphere after recovery of the right hand. These observations demonstrated that a monkey could learn a difficult novel fine motor task after a large lesion of M1 of both hemispheres, although they commented that learning was slower than in the case of intact monkeys on this task. This finding also supported previous observations of learning a new fine motor task after lesion of M1 in one hemisphere and lesion of the pyramidal tract out of the other hemisphere ([92] as reported by Lashley [52]). Moreover, study in one of these monkeys was done with the weighted drawer device after two lesions to the arm areas of left M1. Here, an initial lesion of the entire excitable arm area was completed, which was followed $1\frac{1}{2}$ months later by "undercutting of the newly excitable area of left motor cortex" in a second operation. After this lesion, the monkey learned to open the device only with the left hand as the right hand remained severely impaired for some time after the second lesion, but was eventually used for gross movements such as climbing in the cage. This is consistent with the work from many studies showing that M1 lesions, as well as lesions to the CST at the medullary level, are associated with recovery of gross motor function [44, 54, 55].

Unilateral lesion of premotor areas alone (i.e., with M1 intact) in monkeys has been shown to have minimal effects on fine hand motor function. For example, lesions limited to M2 unilaterally have been reported to have little effect on posture or movement in macaque monkeys [108] or man [85]. However, bilateral lesions of M2 in macaques had much greater effects on posture, produced hypertonia and even clonus in the digits [108]. Although Travis [108] did not evaluate fine motor function in this work, it is likely that fine motor function was compromised. Other work showed minimal effects of a bilateral M2 lesion on hand fine motor function, although there were some effects on upper limb posture/movement due to hypertonia at shoulder and elbow [43]. Later work also demonstrated no deficits in unimanual fine motor tasks after M2 lesions but a deficit of bimanual control if the two hands must simultaneously perform different tasks, such as when mirror-type movements are involved [8, 9]. In contrast, Passingham *et al.* observed that monkeys with M2 lesions also performed poorly in a simple arbitrary task involving raising the arm to receive a food reward [106]. Interestingly, these monkeys performed the task better when performance was triggered by an external stimulus than when required to simply initiate the movement at their own pace. Monkeys with anterior cingulate lesions had similar impairments, but monkeys with LPMC lesions

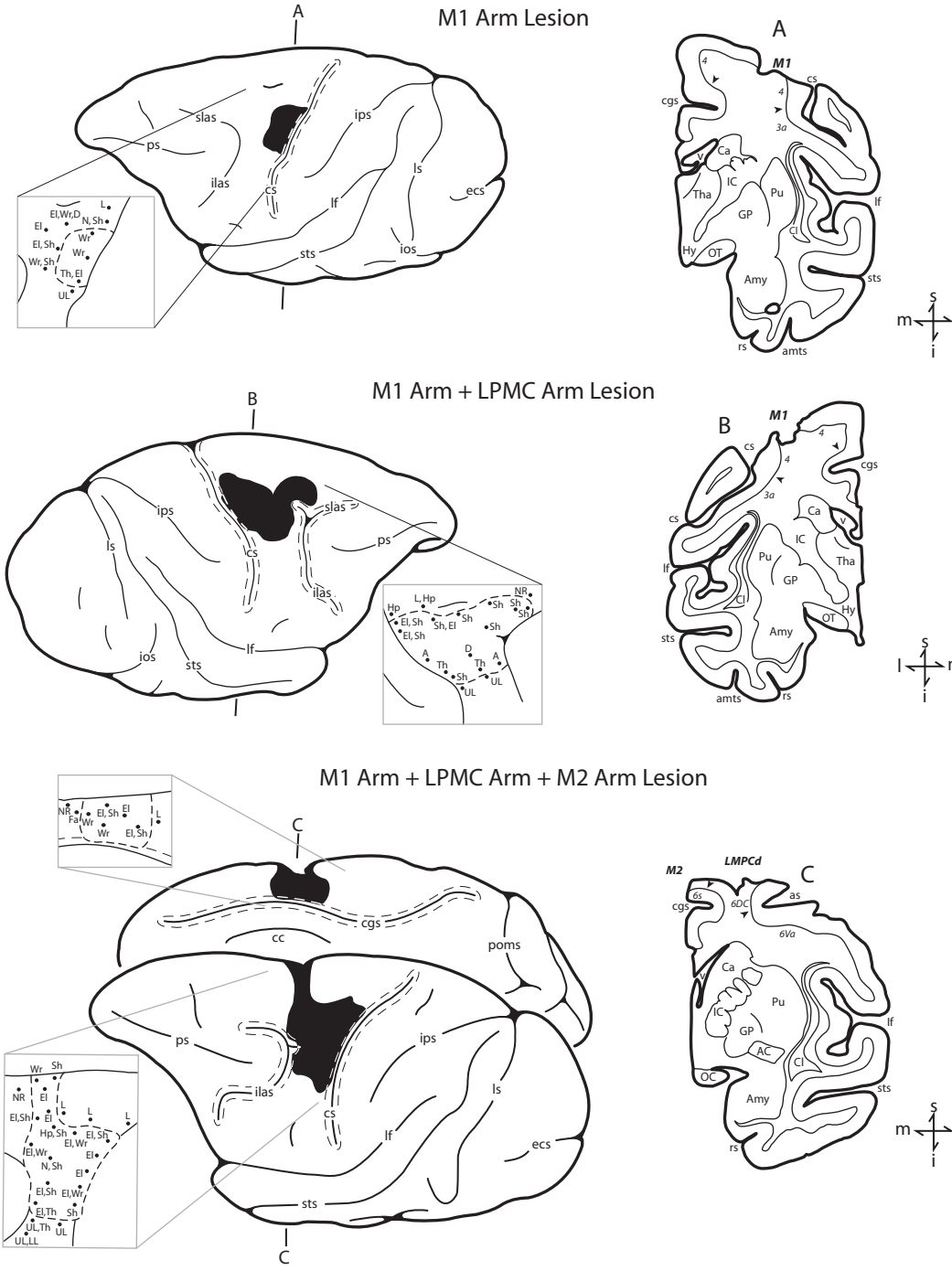

Fig. 5. Lesions of M1 arm area, M1 + LPMC arm areas and M1 + LPMC + M2 arm areas are depicted as performed for studies of volumetric effects of frontal lobe motor area lesions [21]. Arm representations were identified using intracortical microstimulation.

did not. Further study suggested that individuals/monkeys with M2 lesions perform better in response to external cues because they can use these cues as "instructions" [14]. Earlier work by Passingham *et al.* showed that individuals/monkeys with unilateral LPMC lesions without damage to M1 or M2 areas demonstrated deficits in responding to visual cues related to upper limb movements (e.g., pulling and/or squeezing a handle) under certain conditions, but did not have difficulty performing reach/grasp movements to pick up a peanut in a box [41, 42, 82, 83].

We did not find any major reports of investigations into effects of lesions to cortical motor areas on hand motor function in the 1960s [110]. However, there was one study that examined the effects of such lesions to different precentral motor areas on spinal cord distribution of outputs using the standard Marchi method to detect degenerating myelin, as well as the then newer Nauta method that permitted identification of degenerating axons in the spinal gray matter [61]. It was reported that motor deficits following the lesion of the precentral arm motor area were similar to those described previously [106] and that the observations with the Marchi method were also similar to previous findings (e.g., [2]). The novel findings with the Nauta method were that contralateral corticospinal projections from the precentral arm area were found in proximal and distal spinal motor neurons pools whereas ipsilateral corticospinal projections were limited to only proximal spinal motor neurons [61]. These findings suggested that M1 of the undamaged hemisphere may assist in recovery of proximal arm joint motions (shoulder and elbow) but not so for the wrist and digit joints.

7. Training, Rehabilitation, and Recovery

Subsequent work in the 1970s focused on the effects of postlesion training (rehabilitation) on recovery of upper limb strength. From an important and rarely cited series of papers, it was demonstrated that recovery of proximal flexor muscle strength (to 90% of prelesion performance levels) was much better than in distal muscles controlling grip strength (only to about 50% of prelesion performance levels) after unilateral precentral forelimb area ablation [4]. Secondly, similar recovery was possible after bilateral M1 forelimb area ablations, but required 5−6 months instead of three months. Ablation of the remainder of the precentral motor area reinstated the initial paresis for a short time, but recovery of distal strength was to similar levels as after ablation of the precentral forelimb area only [5]. These results suggest that although perilesional M1 and contralesional M1 may contribute to recovery of strength, they are not necessary since similar total recovery can occur without these areas. Surprisingly, however, ablation of the entire precentral motor area in a single surgery resulted in much poorer recovery of contralesional proximal and distal upper limb muscle strength than after serial ablations (i.e., M1 arm area, recovery, then remainder of M1 and/or contralesional M1). Black *et al.* also showed that daily training on the strength tasks with the contralesional arm led to better recovery of upper limb pulling and grip strength [6]. Moreover, starting

rehabilitation training immediately after the lesion was found to produce much better recovery than starting four months after the lesion. It is important to note, however, that the monkeys were trained daily on the same task on which they were tested for recovery. Unfortunately, they did not assess whether training on the strength tasks influenced recovery of fine hand motor functions such as grasping and manipulating small objects, which are important skills in primates.

Following the work of Black *et al.* that focused on strength, there was a return to consideration of fine motor tasks, specifically precision grip and independent finger movements. Passingham *et al.*, following up on the work of Kennard in the 1940s and 1950s, showed that there was no recovery of precision grip after complete unilateral removal of left M1 or M1 and S1 (Fig. 4) in infant rhesus monkeys (age 7 days−3 months) tested 1−2 years after the lesion, despite excellent recovery of locomotion and climbing abilities over 10 months postlesion [81]. Notably, they assessed use of precision grip by using an apparatus in which peanuts had to be removed from holes 2−6 cm in diameter or a cylindrical food pellet was used in a special device such that the food morsel could be "picked out only by inserting the fingers into two grooves (7-mm wide, 21-mm long, 12-mm deep) leading into the well from either side" (see Fig. 1 of Passingham *et al.* [81]). Although all monkeys with M1 lesions would use the right hand to acquire peanuts in the 2-cm hole when first tested, 3 of 4 monkeys with M1 + S1 lesions initially refused to use the right hand to reach for food and required some "training" (passively moving the right hand onto food) to use the right hand in these tasks. Moreover, only one monkey with M1 + S1 lesion (the one not requiring training) could retrieve a peanut from the 2-cm hole and the others were only successful on the 3-cm hole. Testing on the slot apparatus showed that all these animals could retrieve the food pellet with the left hand but only one animal (with a M1 lesion) could remove the pellet with the right hand with the slots in all four tested orientations (i.e., parallel, perpendicular and two oblique angles to the frontal plane of monkey).

These findings prompted an additional study to compare recovery of infants and adults to test the "Kennard Principle" suggesting that cortical damage in infant primates had little, if any, lasting effects on motor function whereas the same lesion in juveniles and adults led to lasting deficits on fine hand and foot motor function [84]. As mentioned above and discussed in the work of Passingham *et al.* [84], although Kennard conclusively demonstrated that infant monkeys show much faster initial recovery than adult animals from a variety of neocortical lesions, the post-lesion survival durations were much longer for infants than for adult monkeys [37, 47−50]. Thus, the question of persistent deficits was not adequately assessed over a similar postlesion survival period in Kennard's work. The same tests applied in previous work [81] were used by Passingham *et al.* to fully assess capability for precision grasp, as well as additional "problem box tests" in adults. All animals were allowed 19−26 months postlesion recovery with no special training (note that the same infants studied in Passingham *et al.*, [81] were included in the 1983 report). Importantly, there were no obvious differences in the performance of monkeys with

complete lesions as infants versus older monkeys on any tests and it was clear that the hand was used crudely when grasping by closing all fingers at once rather than with precision grip. However, all animals showed excellent recovery of locomotion, climbing and jumping (including safe landings). Thus, the results convincingly showed that adults could recover similarly to infants if given sufficient time. Moreover, they concluded that this study confirmed the suggestion that control of fine finger movements requires direct anatomical pathways from the cortex to motor neurons, which exist in the upper limb and foot areas of motor cortex in rhesus monkeys [55]. Indeed, anatomical study of the CST output pathways of sensorimotor areas of the non-lesioned hemisphere to brainstem and spinal cord following removal of M1 and/or S1 in infant monkeys showed no differences when compared to CST output patterns in adult monkeys following similar lesions [99]. Thus, recovery of infants and adults did not occur by establishing new cortical output connections from the undamaged contralesional sensorimotor areas.

A major question arises from the extensive research carried out on effects of lesions to motor cortex in nonhuman primates through the 1980s: What is the mechanism for recovery of voluntary movement control, especially for fine dexterous movements of the hand and fingers? Sherrington *et al.* suggested that since ablation of the arm area in the M1 of one hemisphere produces only temporary paralysis and that further ablations in M1 of the same hemisphere and the other hemisphere (and of S1) do not reinstate the paralysis, the function of M1 had been taken over at a subcortical level [40, 59]. They also observed that stimulation of perilesional cortex did not produce upper limb movements, further suggesting that undamaged M1 did not take over function of the damaged region. In contrast, the smaller lesions induced by Glees and Cole [38] showed that recovery of hand function following ablations of the arm area of M1 was associated with undamaged parts of M1 becoming able to produce arm movements when stimulated. Similarly, Nudo *et al.* have demonstrated that reorganization of perilesional cortex associated with postlesion training of skillful hand movements and concurrent cortical stimulation in squirrel monkeys is associated with better recovery of hand movements [74–76, 78, 87]. It is important to note that in the studies by Nudo *et al.*, the brain lesions were very small compared to previous studies where the entire arm area of M1 or the entire precentral gyrus was intentionally removed. Importantly, however, these contemporary studies suggest that recovery is stimulated by postlesion training/therapy and is accompanied by cortical reorganization in the perilesional cortex as well as altered connectivity from ventral premotor cortex to S1, which implicates a role for S1 in recovery from damage to M1. Surprisingly, ventral premotor cortex connectivity to perilesional M1 regions was not changed, although perilesional M1 neurons are thought to alter motor maps to permit control over muscle groups that were originally controlled by the lesioned area.

Another important question is whether independent digit movements can recover after a complete lesion of the M1 arm/hand area. Many of the classical studies in the first half of the 20th century involved large lesions where the investigators

purposefully damaged the areas deep within the central sulcus to ensure that there were no surviving M1 neurons. For example, Ogden and Franz [79] stated: "To destroy the motor zone lying concealed with the central fissure the white hot cautery was pushed about 6 to 8 mm into the brain substance and carried close to and parallel with the fissure." It seems highly likely that such a procedure would also have damaged neurons of the adjacent S1, yet they reported full recovery of grasping and all fine motor functions of the contralesional arm associated with constraining the less impaired ipsilesional arm and extensive rehabilitation training. Unfortunately, like many studies at this time, there were no quantitative measures or techniques that forced the monkey to use fully independent digit movements for precision grasping of objects. Ogden and Franz [79] also reported that a monkey that did not receive constraint of the less impaired limb and intensive therapy did not show good recovery of grasping and only used power-type grasps (using all digits), which is consistent with the more recent findings [84].

It is generally accepted that recovery of independent digit movements and precision grip are mediated by monosynaptic connections from M1 to hand motor neurons in the spinal cord [55, 57]. However, Murata *et al.* recently reported that recovery of independent digit movements and precision grip was possible after lesion of the M1 hand/digit areas with intensive daily training of the impaired contralesional limb combined with restraint of the less impaired ipsilesional limb [71]. They used ibotenic acid rather than surgical removal of the area to produce these lesions and evaluated reacquisition of precision grip using a dexterity (Kluver) board apparatus with the smallest well being 1-cm diameter. Monkeys were trained before the lesion to acquire food pellets from this well successfully on 1000 trials on two consecutive days. Mean prelesion success rate was about 80% on this well and 83−100% on larger wells. Postlesion performance in the last three days (more than 10 weeks after the lesion) returned to a 60% success rate on the smallest well and 78−100% on the other wells. They used video analysis to qualitatively assess type of grip used. They also noted how postlesion recovery began with gripping raisins between the tip of the index and on the proximal phalanx of thumb, but progressed to grip between the tips of the thumb and index.

We have also reported recovery of independent digit movements and precision grasping using a dexterity board apparatus with a smallest well of 1 cm in diameter in rhesus monkeys with much larger lesions including most of the arm areas of M1, premotor cortex and M2 (Fig. 5) [21]. This work represents an advance over the earlier lesion studies on macaque monkeys that relied primarily on success rates in target acquisition to estimate motor performance rather than temporal, spatial and kinetic measures to quantitatively evaluate the reaching kinematics and hand coordination in both the transport and manipulation phases of grasping [19, 86]. In the lesions we have studied, some of the digit representations in the depths of the central sulcus were spared (Figs. 5(a) and 5(b)). However, there was no intensive daily pre- or postlesion training in these monkeys as in the studies discussed above [71, 74]. Testing in our work was approximately at weekly intervals prelesion and

exactly weekly intervals for the first two months postlesion with only 25 trials with each hand on the dexterity board apparatus (and 15 trials with each hand on another apparatus). No physical constraint of the ipsilesional limb was imposed, but the testing apparatus forced the use of the contralesional limb [86]. Thus, although our intent was to evaluate "spontaneous recovery" we recognize that the limited forced use of the impaired limb likely provided some therapy once/week and may have stimulated use of that hand in the monkey's cage as indicated by observation and a "learned nonuse test" in which either hand could be used to acquire food pellets [20]. However, we did not evaluate location of the gripping surface on the thumb or report on performance in the smallest well as was reported by Murata *et al.* [71]. To investigate this aspect of grip, we have recently reviewed our video recordings and found that monkeys with lesions of arm areas of M1, M1 + LPMC and M1 + LPMC + M2 (Fig. 5) did return to using precision grip (e.g., Fig. 6) and were successful on smaller wells if they were also successful on those wells during

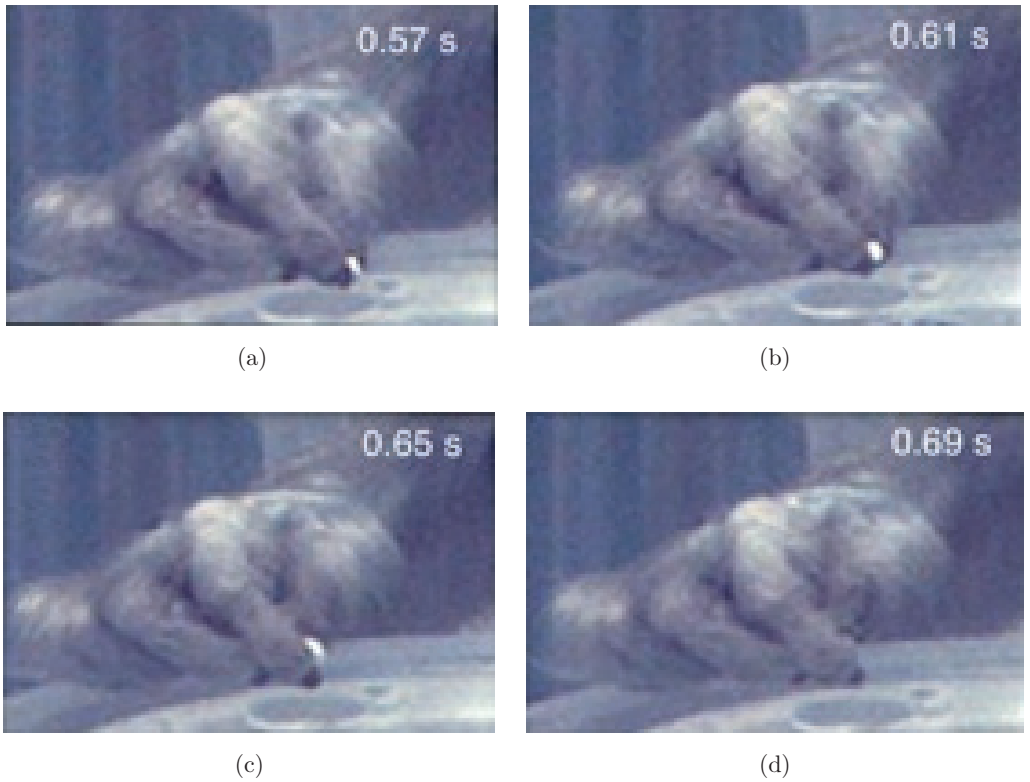

Fig. 6. Performance of precision grasping and manipulation by a monkey with a lesion to arm areas of M1 + LPMC (SDM48 − extent of lesion shown in Fig. 6(c) of McNeal *et al.* [64]. The sequence of video frames shows precision grasp of a food pellet between the tips of the index finger and thumb (a) followed by manipulation the food pellet (b)−(d). Once the pellet is removed from well C (diameter of 19 mm) of the modified dexterity board, it is manipulated to a more secure location on the palmar surface of the distal phalanx of the index. The times shown in each frame represent the time since initial contact with the dexterity board (i.e., 0.12 s spent manipulating the pellet's position on the fingertip by moving the thumb).

prelesion testing. Moreover, there was clear postlesion evidence of manipulation of the pellet while in precision grip to produce a more secure gripping position between the tips of the thumb and index in these monkeys (e.g., Fig. 6). Thus, the monkeys recover impressive ability for precision grip and manipulation of a very small fairly rigid object (0.5-mm food pellet) that is likely more difficult to manipulate than the raisin treat used by Murata *et al.* [71]. An important question in this work is whether M1 neurons deep in the central sulcus are damaged in these lesions and, thus, may subserve recovery of independent finger movements and precision grip. We are currently addressing this issue using combined surgical removal of the M1 arm area and ibotenic acid injected deep along the central sulcus arm area.

An important issue relevant to control of independent finger movements and M1 lesions is that a large body of work suggests that M1 areas controlling an individual finger are distributed throughout the M1 hand area, rather than being localized to separate areas [114]. This is supported by anatomical and physiological evidence concerning widespread inputs to and outputs from M1 hand area neurons (e.g., [15, 25, 94]) and studies of M1 neuron recording showing that activation is distributed throughout M1 hand area [95]. Moreover, short-term inactivation of small regions within medial, intermediate and lateral portions of the hand area in rhesus monkeys showed effects that were not isolated to single fingers and, in general, appeared to be stochastic rather than systematic in their effects on different digits [97]. This distributed organization of M1 neurons controlling the digits means that only large lesions will damage neurons controlling all movements of any one digit and that independent digit movements are likely to recover in the case of small lesions by reorganization of perilesional areas as discussed above. This is also consistent with observations in stroke patients that voluntary contractions of muscles to move a single digit were accompanied by inappropriate contractions in muscles acting on additional digits due to decreased ability to selectively activate certain muscles and suppress activation of other muscles [96]. Indeed, Lang and Schieber [53] concluded that spared cerebral motor areas and other descending pathways allow activation of finger muscles after motor cortex or CST lesions, but do not provide highly selective control due to damage of M1 output.

Overall, given that in many human brain lesions such as those arising from middle cerebral artery (MCA) stroke, which often damage the lateral aspect of M1 and premotor cortex, it seems likely that recovery must depend on reorganization in non-injured brain areas, either subcortical as surmised by Sherrington and colleagues and/or nearby cortical premotor areas as suggested by others [22]. It is this latter possibility that has primarily driven our recent work in which effects of lesions of most of the arm areas of M1 and lateral premotor cortex have been surgically removed to partially simulate the effects of a large middle cerebral artery stroke. In these studies, we have shown that behavioral deficits increase with lesion volume, especially as the lesion is expanded to include the medial motor areas and medial prefrontal areas [21]. Consistent with and expanding on previous work over the past 100+ years, substantial recovery of fine hand motor function, including precision

grasp, occurs even when the lesion includes medial premotor areas. However, we have convincingly shown that when damage is limited to lateral cortical motor areas, which have been shown by others to provide the bulk of CST connections onto interneurons in lamina VII and motor neurons in lamina IX [26, 63], one mechanism of recovery includes enhancement of CST connections from the medially located supplementary motor area (M2) in spinal cord laminae that contain neurons which have lost substantial input from lateral motor areas (Fig. 7) [64]. Importantly, this

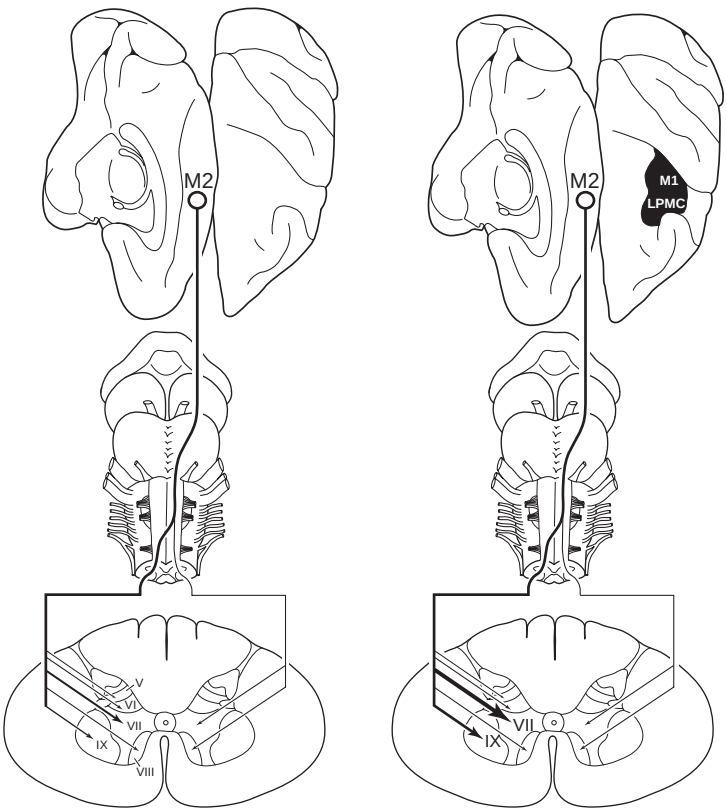

Fig. 7. Summary diagram illustrating the main findings of McNeal and colleagues [64]. The left diagram (a) illustrates the corticospinal projection from the supplementary motor cortex (M2) in the control experiments. This projection originates from the medial wall of the hemisphere (top, hinged to left from dorsal view of cerebral cortex on right) and most descending fibers cross the midline at inferior brainstem levels (middle) ending in the spinal cord (bottom). The relative intensity of the projection to spinal cord laminae is indicated by line thickness and arrow size. Denser terminal projections are represented by increased line thickness and arrow head size. Progressively lighter terminal projections are indicated by progressively thinner lines and arrowheads. The right diagram (b) illustrates the M2 corticospinal projection in the brain injury experiments after motor recovery of dexterous upper extremity movements. The lesion is located on the dorsal view of the hemisphere (blackened area) and involved the arm representation of the primary motor cortex (M1) and adjacent part of the lateral premotor cortex (LPMC). Extensive enhancement of the contralateral projection to lamina VII and IX occurred following the lateral motor cortical injury but not in other contralateral or ipsilateral laminae. (Fig. 13 — Wiley-Liss, Inc., *J Comput Neurol*, used with permission.)

mechanism appears to correlate strongly with recovery of hand/digit fine motor function for grasping small food targets and gross arm function in the form of accurate, fast reaching movements to these targets. Moreover, a deficit of fine hand movement control is re-established for a few weeks if the M2 arm area is lesioned using ibotenic acid (after recovery from the M1/LPMC lesion), strongly suggesting that the M2 arm area is partially responsible for recovery [64]. Reorganization of corticofugal outputs to enhance connections onto brainstem motor nuclei is also likely, and we are currently studying these output connections in the pons where there appears to be a selective increase in M2 connections onto some nuclei.

Another important finding of our work in collaboration with our colleagues at the University of North Dakota is that recovery after lesions to motor and premotor areas in the nonhuman primate is associated with long term activation of microglia and macrophages in the perilesional cortex and cervical spinal cord that continues for up to one year after the lesion [72, 73]. Moreover, marked increases in brain derived neurotrophic factor (BDNF) and its receptor subtypes were also observed in the perilesional area and cervical spinal cord, suggesting that a long-term contribution of neurotrophic factors in the recovery process is associated with establishing enhanced connections between CST fibers from M2 and ventral horn motor neurons. Whether these processes can be enhanced with certain pharmaceutical or physical therapies is an important question. For example, Nogo is a key axonal growth inhibitory protein and pharmaceutical blockade of this protein induces axonal sprouting and function recovery in stroke [56]. Axonal growth stimulators are also targets for current research (for a review of these issues, see [11]).

There are clear and potentially important implications of this work for human patients with brain injury due to stroke or trauma. First, it appears that recovery is possible even after relatively large lesions affecting lateral cortical motor areas if the output fibers of other motor areas such as the medially located supplementary motor cortex are spared. Indeed, middle cerebral artery occlusion is the most common form of stroke and the arm/hand region of M1 and its descending projection fibers are often destroyed [12]. In contrast, M2 resides in the territory of the anterior cerebral artery which is spared in greater than 97% of first time stroke victims [7]. However, this situation does not preclude the possibility of the descending fibers from M2 being injured because they eventually pass through subcortical white matter regions [66] supplied by branches of the middle cerebral artery [101, 109]. Therefore, the application of MRI techniques such as diffusion tensor imaging to quantify whether the descending M2 fibers are spared following lateral cortical injury should reveal whether enhancement of M2 corticospinal connections promotes recovery of hand functions in patients. However, our work has also shown remarkable recovery of hand function after lesions that also include the arm areas of M2 (Fig. 5(c)) and adjacent pre-SMA (see Figs. 2 and 3 of [21]). Thus, reorganization of other cortical (e.g., cingulate motor areas M3 and/or M4 and parietal cortex) or subcortical motor nuclei may also contribute to recovery under such conditions. Finally, we have also shown that many of these monkeys recover to perform consistently at levels equal

to, or even better than during prelesion training. This is likely due to continued task practice since large lesions of motor cortical areas do not appear to abolish well-established motor habits [52] or the ability to learn new hand motor tasks ([92] as reported by Lashley [52]). Collectively, such findings provide considerable support for the idea that favorable recovery is possible following substantial cortical brain damage in nonhuman primates. The clinical question of how best to promote such a recovery in human patients with typically larger lesions using physical rehabilitation techniques (i.e., task performance), brain stimulation (transcranial DC stimulation, repetitive transcranial magnetic stimulation or epidural stimulation) (for a review, see [88]), and pharmaceutical techniques [11] either singly or in combination [3, 28, 80] remains a high priority in the pursuit to enhance the recovery process following motor cortex injury.

8. Conclusions

It is clear from early classical and more recent work that nonhuman primates are able to recover contralesional movement control after small and large lesions of frontal motor cortical areas, especially with some type of intense rehabilitation (e.g., [6, 71, 79]) or even less intense task practice that involves minimal forced use of the impaired limb [21]. Indeed we have observed a very poor recovery of upper limb movements in only one monkey who received a very large lesion affecting the dorsal frontal lobe motor areas and medial prefrontal cortex that also included a large volume of white matter damage [21]. It is quite possible that this monkey would have shown better recovery with intense rehabilitation such as that provided by Ogden and Franz [79]. However, the other monkeys in our study in which the lesion spared at least some cortical motor areas (i.e., cingulate or M2) as well as parts of M1 deep in the central sulcus showed good recovery that was associated with return to prelesion skill levels, or greater manipulation skill levels [21]. In contrast, humans with lesions that affect cortical motor areas commonly do not show such good recovery, especially in terms of grasping and manipulating small objects. Possible reasons for poorer recovery in these patients include: (1) greater subcortical white matter damage disrupting descending corticofugal projections arising from apparently spared motor areas, as well as subcortical damage interrupting the many longitudinally orientated corticocortical axonal pathways that interconnect distant parts of the cortical mantle and subserve the reaching and grasping process (i.e., parietal and frontal areas), (2) greater cortical functional specialization and hand dominance in humans, as reflected in the more developed CST [17, 58] which may affect ability of nonlesioned motor areas to remodel inputs/outputs to take over function of damaged areas, (3) stronger interhemispheric inhibition (associated with greater lateralization) in humans such that undamaged motor areas in the lesioned hemisphere are greatly inhibited and less able to drive neuroplasticity following the lesion and (4) greater effects of emotional depression in humans, leading to lower motivation during rehabilitation.

Subcortical white matter damage is likely one of the most important factors limiting recovery in humans. There are several reports that surgical lesions to frontal lobe cortical motor areas in humans for treatment of cancer, epilepsy and arteriovenous malformations produce only minor or no lasting motor deficits [13, 65, 91]. Damage to white matter is minimized in such surgeries, but can be much greater when the lesion is due to stroke or traumatic injury. Importantly, several recent studies have shown that the integrity of the corticospinal tract at the level of the internal capsule is a strong predictor of motor function recovery after stroke [60, 89, 100]. Thus, even in the case of cortical strokes when there is no loss of blood supply to the internal capsule, damage to the white matter just below the cortical lesion, not gray matter, may be a primary determinant of motor function recovery. Indeed, our work suggests that M2 can substitute functionally after damage to M1 and LPMC if the M2 output fibers are not damaged [64]. Furthermore, in our studies one monkey (SDM64) demonstrated slower and poorer recovery than other monkeys receiving similar (M1 + LPMC arm area) lesions [21] that was apparently due to greater white matter damage that unintentionally disrupted the descending corticofugal fibers arising from M2 that was verified with a tract tracer experiment (unpublished observations).

There are many important implications for future experimentation to improve the recovery prognosis for upper limb motor function in humans. The effects of the various therapeutic techniques discussed above (forced task practice, pharmacological treatments, cortical stimulation) on the neuroplastic response of M2 after a large lesion in the MCA territory that produces poor spontaneous recovery in monkeys would be one useful study. Development of controlled ischemic and hemorrhagic models of MCA stroke in monkeys that are similar to those used in rats would also be helpful because the recovery process from such strokes may differ from surgical ablation, although it will clearly be difficult to control extent of damage in monkeys due to the extensive arterial territory supplied by the MCA [18, 36, 90, 111]. Studies in nonhuman primates are also recommended for preclinical testing of neuroprotective agents [32] and will also be helpful for studies of rehabilitation effects because of the similarity of upper limb use to humans.

After review of more than 100 years of research conducted on the recovery of upper limb movement in nonhuman primates, it is clear that our understanding of the motor recovery process continues to develop. The early work showed that there are many potential neural systems other than the frontal motor cortex capable of effective participation in motor recovery. Although some advances have been made, we are still faced with the daunting task of identifying all neural systems that support the recovery process. Obtaining large groups of patients with isolated injury to distinct cortical motor areas, primarily limited to the gray matter, are conceivably improbable even with access to large patient populations. However, due to the structural homologies of the nonhuman primate and human brain that correlate to the highly developed control of distal upper limb movements [17, 58], there remains great potential to identify contributing factors that lead to specific motor

deficits, pinpoint the mechanisms supporting favorable recovery, and implement potential rehabilitative interventions following isolated motor cortex injury in the nonhuman primate model.

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OPEN QUESTIONS IN COMPUTATIONAL MOTOR CONTROL

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Computational motor control covers all applications of quantitative tools for the study of the biological movement control system. This paper provides a review of this field in the form of a list of open questions. After an introduction in which we define computational motor control, we describe: a Turing-like test for motor intelligence; internal models, inverse model, forward model, feedback error learning and distal teacher; time representation, and adaptation to delay; intermittence control strategies; equilibrium hypotheses and threshold control; the spatiotemporal hierarchy of wide sense adaptation, i.e., feedback, learning, adaptation, and evolution; optimization based models for trajectory formation and optimal feedback control; motor memory, the past and the future; and conclude with the virtue of redundancy. Each section in this paper starts with a review of the relevant literature and a few more specific studies addressing the open question, and ends with speculations about the possible answer and its implications to motor neuroscience. This review is aimed at concisely covering the topic from the author's perspective with emphasis on learning mechanisms and the various structures and limitations of internal models.

Keywords: Computational motor control; internal models; forward model; inverse model; motor learning; feedback; adaptation; motor memory; time representation; reaching movements; trajectory formation; redundancy.

1. Introduction

Computational motor control is a young field of study within neuroscience, and most of the models are still controversial. Therefore, I have decided to review the field in the form of a list of open questions.

The very first open question in neuroscience is clearly the mind–body problem. What is the relation between mental phenomena and physical bodies? We are not going to discuss this question here, since the underlying assumption of the author is that the brain in general and the motor system in particular can be usefully described by means of computational models. The second section addresses this assumption and questions our ability as engineers to reproduce the human function.

The rest of the open questions listed in this review concern the structure and function of the best computational models and the extent of their fit to the actual neural control of movement system.

The open questions structure is aimed at covering a large portion of the quantitative motor neuroscience research and provides a review of the current state of the art in computational motor control. Therefore, each section in this paper starts with a review of the relevant literature and a few more specific studies addressing the open question, and ends with speculations about the possible answer and its implications to motor neuroscience. This review is aimed at concisely covering the topic from the author's perspective with emphasis on learning mechanisms and the various structures and limitations of internal models. The reader is referred to textbooks and more specific reviews for more details and other perspectives [68, 71, 84, 137, 133, 158, 135].

Before we move to the open questions, let me define the notion of computational motor control, and then, demonstrate it by three examples of computational models for the motor system (Fig. 1): (a) The length servo model for the stretch reflex, namely, feedback control, (b) the minimum jerk model as an example of optimality approaches, and (c) trial-by-trial adaptation as an example for internal model adaptation and learning concepts.

Computational motor control covers all applications of quantitative engineering tools, as well as other mathematical tools, for the study of the biological movement control system, which includes the joints, muscles, sensory organs and, of course, the nervous system [68].

Feedback control is one of the basic engineering tools in modern control theory (Fig. 1(a)). As noted by Granit [49], the concept of servo control, as developed by engineers in the last century, is practically as old as experimental physiology,

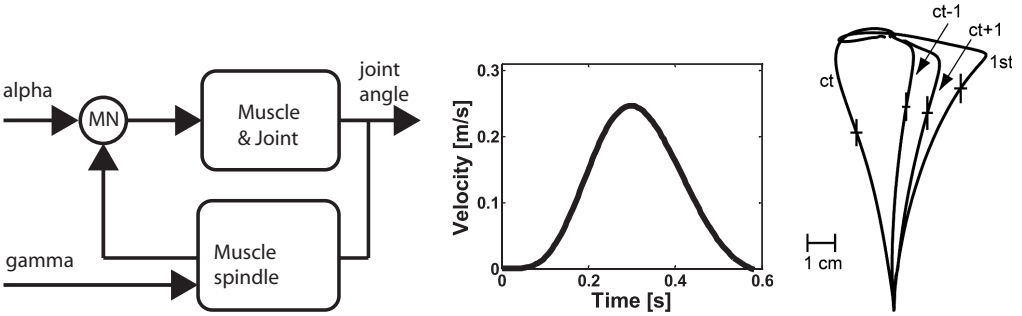

Fig. 1. (a) The length servo hypothesis, illustrating the motor neuron, the muscle and joint, and the muscle spindle in the form of a simple feedback control scheme. The alpha and gamma commands set the desired muscle length/joint angle and the reflex loop act to follow the desired trajectory. (b) Typical velocity profile of human reaching movement, well fitted by a minimum jerk trajectory as well as many other optimization schemes. (c) Deviation from a straight line at the first exposure to force perturbations, after adaptation (ct-1), during a catch trial (ct) and during the following trial (ct + 1), demonstrating trial by trial adaptation mechanism, adapted from [147].

and could be traced back to Claude Bernard's idea about the constancy of the internal environment (1865). The stretch reflex beautifully matches the engineering classical servo model of negative feedback: the muscle spindle reports muscle extension to the spinal cord, and this information returns through a single synapse over the motor neuron of the same muscle in the form of a motor command to shorten that muscle. Basic control theory tools such as mechanical models to the muscles, frequency response and stability analysis were extensively used to explore this system [94, 97].

Reaching movements are basic point-to-point arm movements. They are frequently used to test various computational models for the motor system. Such models started from basic kinematic observations about the fact that we typically perform straight line movements, using extrinsic coordinates rather than joints coordinate to plan our movements [1, 104]. In addition, it was found that the tangential speed of reaching movement is bell shaped; namely, the velocity smoothly increases and decreases during the movement (Fig. 1(b)). To account for these properties, various computational models were proposed. In these models, we assume that the motor system is optimal in some sense, and search for the optimization criterion that provides trajectories most similar to the observed arm movements. Among models which minimized smoothness, the minimum jerk model is probably the most successful and simple model that accounts for the straight line and bell-shaped speed profile [40]. However, various other models successfully described the same properties using other criteria [150, 8, 143]. Another type of study considered computational models of the muscles and reflex loop's nonlinear properties to account for the observed smooth bell-shaped speed profile of reaching movements [51, 70, 6, 81].

Adaptation is a prominent property of biological systems. Reaching movements were found to be extremely useful in exploration of adaptation and learning and the related computational models. The seminal study of Reza Shadmehr and Sandro Mussa-Ivaldi [134], which became one of the most cited papers of the Journal of Neuroscience, demonstrated that people tend to keep the reaching movement properties (e.g., straight line and bell-shaped speed profile) at the face of external force perturbations. They found that, during this implicit adaptation to force perturbations, subjects used intrinsic coordinates (joint coordinates) when extrapolating from one region of the workspace to the other. Numerous studies followed this influential work explored the capability of the brain to adapt to various force fields and tested various hypotheses in the form of computational models. The most prominent concept in these studies was the simple idea of adaptation by minimizing error from trial to trial [128, 27, 147], as depicted in Fig. 1(c).

Using reaching movements, and later other movements, such as lifting tasks [36], bimanual adaptation [78], and adaptive locomotion [20], the study of computational motor control progressed and used concepts of adaptive control and learning theory to account for the biological control of movement.

2. Can We Build a Robot Indistinguishable from Human in Its Motor Control Capabilities?

Turing [149] proposed an elegant test to probe the intelligence of computers. In the Turing test, an interrogator presents written questions, by means of teleprinter, to two examined entities: a computer and a human being. If the interrogator cannot distinguish between the two entities after extended conversation, we would conclude that the computer is intelligent. Numerous pages of criticism and interpretations were written about the Turing test, e.g., [42, 114]. In this review, I address the motor system; therefore, I wish to concentrate on one criticism of the original Turing test which addresses the linguistic limitation of the original test, and asserts that the ultimate test is to build a robot indistinguishable from humans in all the aspects of its behavior. This is actually the gold standard and a necessary condition for any computational model: can we replace the actual measured data with simulation based on our best computational model, such that the replacement will be indistinguishable?

We have focused on hand movements in one dimension and developed a Turing like handshake test for motor intelligence [69, 75] providing a metric to evaluate human-likeness. Another similar method to evaluate human machine handshake likeness has recently been developed by [47]. It is important to note that the Turing test is based on subjective answers of a human interrogator, while model testing is usually based on objective comparison of measured and simulated data. However, with multiple tests of various individuals and conditions any limitation of the computational model will eventually be exposed.

The implications of a positive answer to this first open question are enormous, scientifically and practically, in building human-like robotic devices and in the design of artificial limbs and assistive robotic devices which will interact naturally with humans. Altogether, the first open question is essentially the ultimate open question of computational motor control: can we build a computational model accounting for any possible perturbation and observation of the motor system? The study of computational motor control hypothesize a positive answer, and therefore, the rest of the questions address specific aspects and instances of this desired ultimate computational model.

3. Does the Brain Employ Internal Models of the Body and the Environment?

The notion of an internal model in the wide sense asserts that the brain contains some information about the controlled system, namely the musculoskeletal system and the external world. Most scientists cannot argue against internal models when so broadly defined, as the phenomenon of adaptation is well documented, and it clearly indicates that the brain employs motor memory or expectations about the world which can be termed internal models.

The controversy begins when someone tries to draw an input−output diagram and propose specific structure of the internal model which can be tested and sooner or later refuted. Proposing refutable hypotheses is the best way to promote science, and therefore, this kind of controversy is constructive. I will review here some of the prominent structures that were proposed for the internal models, and then discuss their implications to science, medicine, and technology.

Cyberneticians use feedback control to describe the motor system (Fig. 1(a)). However, with the progress of control theory, and in particular, the notion of adaptive control theory on the one hand and experimental evidence for adaptation in human behavior on the other hand, it was suggested that the feedback controller has to be adaptive [94], or alternatively, proposed that the brain can control the muscles without feedback by learning the inverse map of the controlled system [60]. Figure 2(a), demonstrates the notion of an inverse controller: It is simply the inverse of the controlled system. Kawato [76] proposed an elegant way to combine feedback control with an inverse model — feedback error learning, which is illustrated in Fig. 2(b). The feedback error learning model solves two problems of the simplified feedforward inverse model control of Fig. 2(a). It incorporates feedback with all its inherent advantages (noise rejection, insensitivity to changes in parameters etc.). In addition, it uses the feedback controller output instead of the output error as an error signal, and thus solves the problems of error signal propagation [72, 65]. Moreover, Kawato *et al.* [131] proposed that the inverse model is implemented in the cerebellum. They followed the studies of

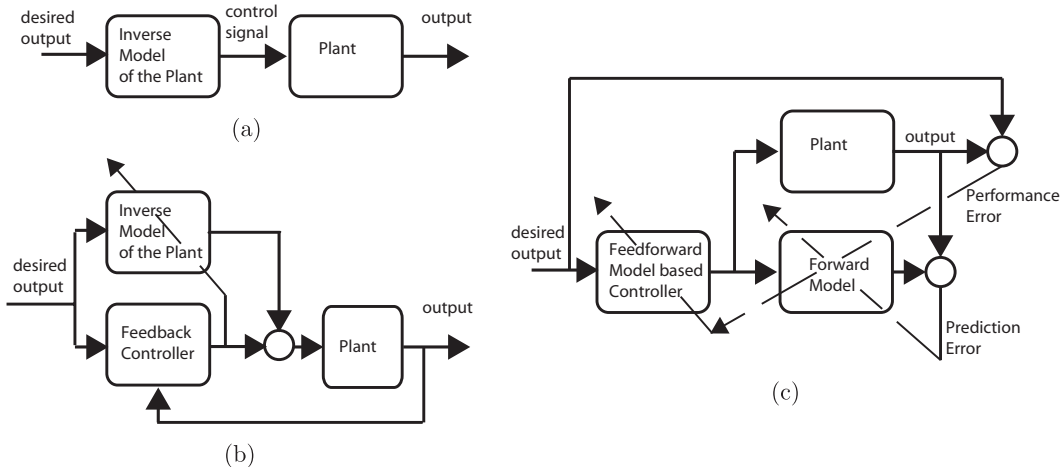

Fig. 2. (a) An open loop control scheme with an internal inverse model as the controller generating the control signal to operate the plant and generate an output similar to the desired output. (b) Feedback error learning (following Kawato [76]). The control signal is the sum of standard feedback controller and an inverse model, where the inverse model is being adapted using the feedback controller signal as motor error. (c) Distal Teacher (following Jordan [64]). Control scheme similar to (a), with an additional forward model which is adapted using the prediction error and is used to propagate the performance error back to teach the inverse model appropriately.

Marr, Albus and Ito [61] and suggested a detailed specific model using modern computational tools of artificial neural networks. The notion of inverse model was later extended to multiple modes in to account for multiple contexts and complex mapping [160], or to account for multiple inverses in the case of redundant systems [73].

Another elegant solution to the problems of error propagation to teach the inverse model is the distal teacher [64]. This approach employs, in addition to the inverse model controller, another type of internal model, a forward model. A forward model generates an estimation of the output given the control signal. In the distal teacher approach, the forward model is trained in parallel to the inverse model; the performance error is then propagated through the forward model to obtain motor error that the inverse model adaptation algorithm can use, as depicted in Fig. 2(c). In this approach, the forward model is learned by minimizing the prediction error, and then it is used to transfer the performance error to the coordinates of the controller, and therefore serves as a teacher to the controller. In this sense, mental practice can be used to train the controller. In experiments that require mental practice, one should also distinguish between implicit and procedural knowledge, and carefully choose the instructions to the subjects and the measure of their success: either what they say or what they do after the mental practice [4].

Forward models are learned from practice and can generate predictions for the consequences of our own motor commands [38, 37]. The literature mentions at least three flavors of these structures: predictor, state estimator, and distal teacher [67]. Figure 2(c) illustrates the possible role of the forward model as a distal teacher [64]. In studies of grip force adaptation, it was demonstrated that subjects can predict the required grip force and a forward model was proposed to account for this behavior [37]. Forward model as state estimator was demonstrated to be plausible experimentally [159], and is used in current state-of-the-art computational models as an essential part of optimal control scheme [133].

The neurophysiological basis of internal models is under research. Among the regions of the brain postulated to be involved in forming and housing, the internal models are the motor cortex [89, 113] and the cerebellum [58, 131, 59, 121, 22]. These studies can shed light as to the location of the postulated internal models but cannot provide a direct evidence for their existence. In my opinion, the best evidence for internal models comes from psychophysical experiments, in which the limitation of our ability to adapt or transfer are quantitatively exposed, informing us of the coordinates and structure of the internal models.

Recent studies employed this notion of internal models with other tasks, such as using tools [24, 58], bimanual coordination [78], locomotion [20, 123], and lifting [15, 36, 95]. Altogether, I find the notion of internal models extremely useful to generate testable hypotheses and represent our knowledge about the motor system. In fact, many of the open questions in this review refers to the structure, capabilities, and limitations of these internal models.

4. Is the Brain Capable of Representing the Flow of Time?

A system is capable of representing time, if it is possible to extract the time, t, from its state [74]. Numerous studies suggest the existence of explicit timing structures in the brain. Accurate musical performances are frequently explained as being based on biological clocks or internal timekeepers [112]. According to Ivry [62, 140], there is evidence for the involvement of many neural structures in the task of time representation, including the cerebellum, basal ganglia and some cortical structures. Time representation has been extensively discussed in the context of neurophysiology, computational models and behavioral studies [156, 154, 77]. However, within the context of adaptation to time-varying force perturbations, all the attempts to expose such time representation failed [74]. This clearly indicates that the motor system does not use time representation for motor adaptation. Current evidence suggests that the motor system employs only state representation, namely position and its time derivatives, such as velocity and acceleration, for adaptation to force perturbations [74, 21]. This evidence is relevant also to the structure of internal models discussed in the previous section as it limits their possible structure to mapping based on position and velocity, refuting the option of rote memorizing of time dependent control function [21]. Adaptation to a delayed force field [88], estimation of stiffness with delay [109, 107, 119, 120], or even assessing simultaneity, does not necessarily require representation of time in the form of an internal clock. These can all be accounted for by regression over force and position variables [107, 109, 118].

In the previous section, I discussed a special type of internal representation, the forward model [103, 67, 37]. This representation can be used for prediction of the outcome of our motor command, and importantly, it is most suitable for describing the internal representations of delay [41]. The cerebellum was proposed to host both internal models and time representation, and therefore, Diedrichsen *et al.* [22], have recently explored this specific question with a special task that involves timing and transfer. They conclude that the cerebellum is responsible for state estimation while timing aspects of the task are being processed in other areas, such as the planum temporal. An interesting speculation in the discussion of this paper asserts that timing may be processed in a way similar to internal speech.

As discussed in the seventh open question about learning and adaptation, it is possible that time representation is not used for adaptation, but instead, it is constructed by a dedicated learning mechanism for specific goals such as music performance. However, another alternative is that all the instances of apparent time representation are simply a disguised state representation. Only careful analysis of the generalization capabilities and accurate temporal transfer can potentially answer this open question with its interesting theoretical and practical consequences, e.g., for human-machine interfaces, teleoperation, and robotic surgery [110, 108].

We have noted two exceptions to the lack of evidence for time representation in the motor system. In a recent study of probing perception of simultaneity, we found that subjects reported the distance between two events based on the time between them and not based on the state simultaneity [117]. However, this case clearly differs from adaptation to force perturbations as it probes the perceptual level rather than the implicit motor adaptation mechanisms. In a careful study of rhythmic movements, we have recently found that movement frequency — or timing — is tightly controlled, even when explicit feedback regarding movement frequency is not given [9]. Indeed, even when healthy individuals misestimated the speed and the amplitude of their rhythmic movements when no visual feedback was given, there was little change in the frequency of their movements [87]. This kind of findings support the hypothesis that time keeping mechanism is involved in the generation of rhythmic movements. However, this kind of time representation could be limited to pattern generators that are based on spinal cord coupled with arm dynamics. Thus, the option that the central nervous system does not employ time representation for implicit motor adaptation is not refuted.

5. Does the Motor System Use Intermittent Control?

In intermittent control, instead of continuously calculating the control signal, the controller occasionally changes the control signal at certain sparse points in time, according to the control law. This control law may or may not, include feedback, adaptation, optimization, or any other control strategy. When, where and how does the brain employ intermittency as it controls movement? These are the open questions addressed in this section.

Evidence for intermittency in human motor control has been repeatedly observed in the neural control of movement literature [26, 35, 54, 105, 106, 141, 156, 45]. Moreover, some researchers have provided theoretical models to address intermittency [8, 17, 18, 54, 46]. Nevertheless, the vast majority of current models involve continuous control, e.g., [148].

Intermittent control is used in engineering systems in very cheap and simple systems, such as the thermostat in many home appliances, as well as in sophisticated systems with large delays or extensive processing time requirements [46]. Intermittent control is at the base of engineering theory of switched systems [3, 93, 53, 90]; in these systems, otherwise unstable systems can be stabilized [90, 43]. Several characteristics of the motor control system suggest that one should expect to find intermittent control strategies that minimize the effort of the central nervous system and effectively exploit the spinal cord as a channel of information transmission. These include delays in signal transmission caused by neural processing and conduction time, and the hierarchical nature of the system in which the spinal cord provides communication between the peripheral and the central nervous system. Indeed, evidence for the existence of intermittent control is provided by a wide

range of studies. Measurement of hand movements in tracking a continuous moving target clearly demonstrate rapid movement followed by stops [105, 54, 101, 141, 102, 106, 100]. Some studies explained the intermittent nature of tracking movements by a refractory period of the central nervous system [106], or "step-and-hold" strategy where exceeding an error threshold generates movements [54, 101, 100]. Intermittent control is also at the basis of models for error correction submovements in reaching [57, 34]. It was suggested that the neural basis of intermittent control during tracking tasks is implemented within the cerebellum-thalamus-cortical loop [52, 102, 151] or within a basal-ganglia-cortex-cerebellum distributed processing modules for reaching [57]. Intermittent control is not restricted to displacement of the hand, rather, it is also evident during isometric force tasks [139, 151] and combined tasks such as tracking a target while experiencing forces [141], switching between motion and force control [152], as well as in handwriting and drawing [152, 129]. Intermittency is also apparent in many models addressing biological hierarchical systems, where the higher level sends intermittent commands to the lower level, e.g., to switch between oscillatory activities in human handwriting [138] or to perform complete arm movements in the octopus, where the basic motor program was found to be embedded within the neural circuitry of the arm itself [145].

Intermittency has also been observed in rhythmic movements [125, 26]. Doeringer and Hogan [26] specifically explored the proposition that vision is contributing to nonsmooth intermittent control. They found that vision is not the major source for the lack of smoothness in this type of movement. It was found that the level of intermittency in rhythmic movements depends on the frequency of movement in the sense that there are two types of movements. Low-frequency movements are more discrete-like and high-frequency movements are more rhythmic-like [86]. We have recently found that the switching between these types of movements does not always occur at the same frequency. When the movement frequency was gradually increasing or decreasing, we found a reverse-hysteresis behavior in the frequency at which the subjects switched from one movement type to the other. This phenomenon can suggest intermittent control, in which the switch time depends on the movement frequency in a predictive fashion [85].

Another possible example for intermittent control in the motor system can be found in the Minimum Acceleration Criterion with Constraints (MACC) model for the control of reaching movement [8]. As described in the beginning of this paper, reaching movements were studied extensively under the assumption that biological systems evolve to find optimal solutions. Therefore, multiple cost functions were suggested to be candidates for the optimization, and all of them produce the characteristic bell-shaped trajectories of movement velocity. These include minimizing jerk, torque change, and noise [150, 24, 40, 143, 55]. Traditionally, solutions to a minimum criterion involving kinematic quantities have been calculated analytically using the Euler-Poisson ordinary differential equation [124]. The analytical solution for the minimum acceleration criterion (MAC) shows nonzero acceleration

at the boundaries. This contradicts the observed hand rest of the reaching movement before and after the movement, and therefore, the MAC was rejected, paving the way to the minimum jerk model [40]. Stein *et al.* [142, 143] indicated a few-limitations of the minimum jerk model and suggested that MAC based trajectory smoothed by a second order filter (muscle) are quite similar to minimum jerk trajectories. Nevertheless, the MAC model has not been seriously considered since. Ben-Itzhak and Karniel [8] proposed a remedy to the MAC by adding acceleration boundary conditions and developing an analytical solution based on the Pontryagin minimum principle [116]. To find a physiologically plausible solution, we also assumed constraints on the maximum and minimum jerk values, and called this criterion a "Minimum Acceleration Criterion with Constraints" (MACC). The MACC based trajectory consists of three segments of constant jerk signal. Precise details, as well as the analytical proof, are provided in [8]. In a first-order muscle model, the control signal is the first derivative of the force. Since the force is proportional to the acceleration, the control signal is proportional to the jerk. Thus, the MACC predicts bang-bang control at the jerk, namely, an intermittent control signal. A particular minor application of the MACC is in detecting onset of movement [14] which can be useful for behavioral neuroscience studies requiring accurate onset detection. Recent measurements in the cerebellum found clear evidence for an intermittent-control strategy [91, 161]. In these studies, it has clearly been shown that the activity of cerebellar Purkinje cells demonstrates bistability — bursting activities separated by pauses.

The concept of intermittence control has recently been studied for the control of inverted pendulum [92], and a thorough review of such a computational theory for intermittence control was written [44]. These and other models of intermittence control should be further extended to provide specific predictions for neural activations in various levels of the motor system. Whether neural recording will support such predicted transitions are the open questions to be explored. The implications of a positive answer include the improvement of movement disorder diagnostics, and the design of optimized haptic human robot interfaces. This could be utilized by concentrating on the relevant transition times in the motor command.

6. Does the Motor System Represent Equilibrium Trajectories?

One of the possible underlying mechanisms for intermittence control that was discussed in the last section is the threshold phenomenon. The threshold phenomenon is observed in each and every neuron and muscle tissue: every excitable cell in the body requires a minimum value of depolarization in order to generate an action potential.

Feldman [32] proposed that this basic threshold phenomenon governs the operation of motor neurons. These neurons are interconnected with the muscle and muscle spindles of antagonistic muscle groups, and thus, enable the higher

level of the control hierarchy to send motor command about the desired limb equilibrium position. This is achieved by determining a parameter he called lambda (λ), which represents the actual threshold of neural activation in the system. The reader is referred to the textbook [84] and literature for support [32], and criticism [33, 111] of this theory. One limitation of the lambda model is that there is no simple relation between the value of lambda and limb position, since that will depend on the load, and may require in some conditions complex equilibrium trajectories [7, 19].

Bizzi *et al.* [115] led a series of studies in which a monkey had to reach a target without proprioception with or without perturbations. The results clearly demonstrated that the arm continues to move towards the target as soon as the obstacle is removed. These results support a theory according to which a stable equilibrium point is generated by the nervous system. Moreover, this equilibrium point can change with time and generate an equilibrium trajectory [11, 115]. Equilibrium point control was examined by Gomi and Kawato [48] who measured the arm stiffness and found clear evidence against the hypothesis that the brain sends as a motor command only an equilibrium-point trajectory similar to the actual trajectory.

We have opened this review with the seminal study of Shadmehr and Mussa-Ivaldi [134] which demonstrated adaptation to force perturbations and after effects of learning in catch trials. That study, as well as many other adaptation studies, clearly demonstrated that equilibrium points or equilibrium trajectories are not sufficient to account for our motor behavior, shifting the research from the lower reflex loop to the level of internal representation and the structure of internal models. Nevertheless, the question is still open since it is possible to assert that equilibrium trajectories exist, and that they are adaptive. There were only a few attempts to combine these two approaches, namely equilibrium point control and adaptation, e.g., [50]. Thus, a computational theory of threshold control, e.g., based on the lambda model, which will account for the rich literature about adaptation to force perturbations has yet to be developed.

7. What is the Difference Between Learning and Adaptation? Structural–Temporal Hierarchy of Wide Sense Adaptation

Adaptation in the wide sense (WSA) is accommodation to the environment. In other words, any processing of sensory information that eventually changes the motor behavior in one way or the other is WSA. Figure 3 presents a map of four instances of this phenomenon: Feedback, adaptation, learning and evolution, where sensory information is integrated and employed to change the control signal in various techniques and time scales. There are some clear boundaries and parallels to engineering concepts: e.g., between feedback that refers to signal flow, and adaptation that refers to changes in parameters, and between evolution and the other instances of WSA. However, the neural implementation of skill learning and

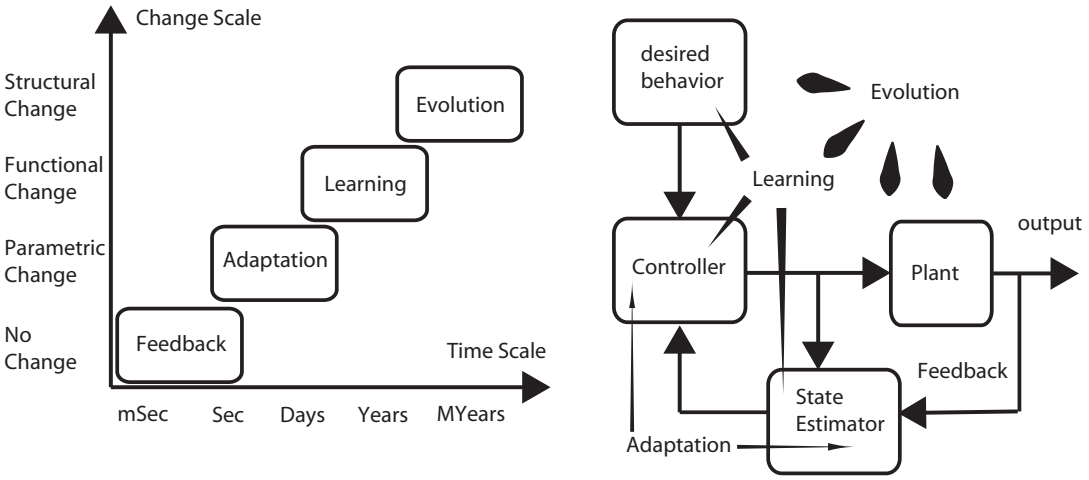

Fig. 3. The temporal structural hierarchy of wide sense adaptation in the motor control system. Feedback, adaptation, learning and evolution are instances of wide sense adaptation where sensory information is integrated and employed to change the control signal in various techniques and time scales. Left: The hierarchy on the temporal structural space. Right: Block diagram of control system demonstrating feedback, adaptation, learning and evolution. Adopted from [68].

other types of learning, and their specific structural and temporal structures, are the open questions discussed at the end of this section. I start with a description of the system approach, and then, I will clarify the scope of each part of this structural temporal hierarchy, and address each type of the WSA separately.

Figure 3 demonstrates the structural−temporal hierarchy in a block diagram. When we think about a control problem we usually have at least two systems: The controller and the controlled system. For example, if we wish to control the position of the hand, we have the controlled system on the one side, i.e., the relation between the neural command to the muscles and the position of the hand, and the controller on the other, i.e., the relation between the intended movement and the neural signals to the muscles implemented by the brain. Other distinctions are possible, such as considering the muscles as part of the controller, as nicely illustrated in the equilibrium point control theory.

A prominent feature of the biological system is to use the sensory information about the actual position of the hand in order to improve the control of its position. This simple idea was used by engineers from the beginning of cybernetics (in part following observation of nature), and was later developed to include also adaptive control. We follow the engineering terminology, use it to define a hierarchy of methods to improve the control signal, and then try to use it to describe the brain as it controls movements. The basic idea of this hierarchy was first presented in [71], and later accurately defined in [68]. Here, I review the main definitions, and present the open question about the distinction between learning and adaptation.

7.1. *Feedback*

We refer to a system as feedback controlled when sensory information is fed back to generate the control signal during the performance of the task. Figure 1(a) describes the notion of feedback in a block diagram. The signal flows from the sensory system to the control system. This path could be long or short depending on the specific system; however, there is no change in the control system, and the changes in the control signals are the result of changes in the sensory signals. In the biological system, the shortest path is typically described as the feedback reflex loop which includes a monosynaptic pathway. However, there is a shorter pathway for feedback within the muscle. The simple mechanical property of stiffness, i.e., the force being proportional to the length of the muscle, could be referred to as feedback control, since the control signal — the force — is influenced by the sensory signal and the length of the muscle. This last example demonstrates a limitation of the engineering approach: the blocks usually hide the detailed structure, and therefore, if we define the control signal as neural input we would never note the internal feedback loops within the muscle and joint. However, there is always a tradeoff, and the simplicity we obtain from this approach helps us in clarifying the notions. It should be noted that the hierarchy described here, for a specific level of abstraction, could be multiplied within each block. Let us summarize this discussion with a formal definition of feedback control: Feedback control of a given input−output system is the usage of the output signal in order to generate the control signal in real time, thus, the only delay is generated by the propagation of signals through the channels and the control system. Figure 1(a) captures the main properties of feedback, namely "signal flow in real time" and "no structural change in the system, only flow of signals."

7.2. *Adaptation*

Adaptive control is a control strategy where the controller can change its function to accommodate changes in the controlled system or in the environment, see e.g., [5]. Here, not only the signals are changed, but the control system is also changed based on the sensory information received. These changes in the system are typically slow when compared to the time scale of the feedback. Figures 2(b)−2(c) and 3(b) describe various instances of adaptive control systems. The controller includes a finite set of adjustable parameters; an adaptation algorithm observes the flow of signals to and from the control system, and determines how this set of parameters should change to improve some measure of performance. This third system — the adaptation algorithm — is implicit in the dashed or dot-dashed lines and is not drawn in a dedicated box in these figures. Let us summarize with a formal definition: Adaptive control is the change in the parameters of the control system generated after observation of previous control and sensory signals in order to improve the future performance of the system on a well-defined task or measurements of performance.

7.3. *Learning*

Learning generates a completely new behavior, as in skill learning, or employs a completely new strategy to achieve a known behavior. In both cases, the controller may change its structure. This is in contrast with adaptation, which refers to a change in parameters of the controller that improves the performance in certain types of existent behavior, without any structural change. Such structural changes in the biological system may include the recruitment of new brain areas or generation of a new neural circuit for specific task, which, in turn, cause behavioral implications such as change in the speed accuracy tradeoff [122]. In artificial systems, the controller may be replaced with another controller. At this point, our technology does not provide an effective learning machine, and it is highly possible that observing the biological system and modeling the neural control of movement may generate new control strategies that would later be used for artificial intelligent control. Later, these will be perfected by control engineers and return to serve as models for the brain. In summary, learning control is a structural change of the control system in order to generate a new type of behavior.

7.4. *Evolution*

In the proposed hierarchy, evolution is the last resort. It may take many years, and it can potentially generate the largest change due to the evolution of a new species or in the engineering term, a new kind of controller. Evolution is an arbitrary change in the controller that can include any change in structure, function, connectivity, parameter values, learning algorithms and adaptation protocols. The best change is chosen by mutation and then survival of the fittest, and therefore, this process may be extremely long.

Altogether, the distinction between feedback and adaptation, and between learning and evolution, is quite clear and well defined, whereas the distinction between adaptation and skill learning is still a subject of active research both about the computational representation, and the neural implementation and the engineering counterpart in state of the art artificial learning control literature.

8. Is the Neural Control of Movement Optimal? In What Sense?

In the temporal−structural hierarchy of wide-sense adaptation, we have seen that sensory information is used to improve the performance of the motor system. However, the desired performance was not directly addressed. A different line of research cares less about the process of learning and adaptation and more about the desired outcome, typically under the assumption that after long practice the system converges to the desired outcome. It is important to note, that any desired outcome can be referred to as optimal (e.g., by defining optimal behavior in the sense of being close to that specific desired outcome). Therefore, the research concerning optimal motor control should consider three open questions for each task being studied: (a) Does the motor control system strives to reach a specific optimal behavior? (b) Does

it actually obtain the optimal behavior in certain conditions? (c) What is this specific optimal behavior? The last question could be also phrased as: In what sense is the behavior optimal? or: What is the minimized cost function? Finally, since we posed this question for each and every task, we can also ask about the generalization and transfer within and between tasks.

Three branches of motor neuroscience use optimization techniques and terminology: trajectory formation studies, optimal feedback control, and Bayesian modeling studies. In trajectory formation studies, the question is typically which optimization criterion will predict the observed arm trajectory, e.g., minimum jerk [40], minimum acceleration [8], minimum object crackle [25], minimum hand jerk [146], minimum torque change [150], and minimum end-point variance [55].

Optimal feedback control is well developed in control theory [82] and has recently been used successfully in modeling human movement control [148, 23, 132, 136]. The main challenge within this framework is to derive the optimal control signal with real nonlinear time-varying biological systems, given specific cost function and the assumptions as to the structure of the noise.

Optimal feedback control is typically based on state feedback, and requires a state estimator which includes a forward model. The idea that the brain may employ state estimation to optimally combine sensory and predictive information was supported by many studies in the last decade [154, 99, 79]. Since optimal feedback control schemes typically use a simple feedback controller, an inverse model is not always required. Instead, the desired trajectory could be implicit within the solution of the optimal control law, accounting for the observed changes in the so-called desired trajectory during adaptation [28, 63]. An open challenge in this field is to develop adaptation algorithms to learn the forward model and an optimal controller which minimizes the cost function at the same time. For example, Mazzoni and Krakauer [96] showed that even when subjects can explicitly perform properly within visuomotor rotation task, they continue to learn the rotation implicitly. These kinds of studies facilitate the constructions of a complete model accounting for all the ingredients of optimal feedback control. Another interesting perspective of optimal feedback control is the fact that it naturally presents itself in a stochastic environment resolving the redundancy problem (see the last open question), by facilitating large variance in the irrelevant directions, also referred to as uncontrolled manifold [66, 130].

Bayesian modeling studies observe the behavior as optimal in the sense of using prior information about ourselves and about the environment (aka internal model), and combining this information with sensory feedback in an optimal way to combine a posterior state estimation. The question about structure of internal model or the sense of optimization is replaced with the selection of relevant variables and extracting or postulating the probability distribution of the prior. Here, I just mention this wide and successful line of study, and the reader is referred to the literature for many examples of successfully modeling various behavioral results, e.g., [144, 79, 31].

9. Does Motor Memory Represent the Past or the Future?

It was suggested that the purpose of memory is to plan for the future rather than to remember the past [2, 29, 127]. This distinction was made with regards to episodic memory. However, such a distinction is also of interest for motor neuroscience, and in particular in the context of motor memory where the concept of forward model is frequently used to describe this exact phenomenon. Namely, a forward model allows the motor system to use the past experiences in order to predict the future.

As described in the opening of this review, extensive research has been performed concerning the ability to adapt to force perturbations during the execution of reaching movements. This methodology was proven most useful in exploring issues related to motor memory [80, 12]. This finding was replicated in different experiments, demonstrating that people learn to adjust motor commands to compensate for disturbing forces depending consistently on the state of motion of the limb [126, 39, 134, 38, 83, 158]. Two main features of memory, consolidation and mental practice, were also studied in the motor control literature [80, 30, 16].

In all these studies of motor adaptation to force perturbations during reaching movements (see Fig. 1(c)), the trial by trial adaptation is based on the past in the sense that the expectation for perturbation in the next trial is generated by a weighted sum of the perturbations in the past few trials. In contrast to this well-established observation, we have recently tested the nature of predictive control during a lifting task and found that in the case when the weight of the object increases from trial to trial, the expectation extrapolates and essentially predicts the future weight of the lifted object [95]. Similarly, when performing a rhythmic task that requires a continuous increase or decrease in movement frequency, participants changed the type of their movement (from discrete-like to harmonic and vice versa) in a predictive fashion, apparently based on the expectation that the required frequency will continue to change in the future [85]. The exact conditions in which we predict the future and the conditions in which we use past average are still open for future investigation.

This open question could be related to the structure of internal models. Let us consider the forward model which predicts the expected sensory outcome of specific motor command. On the extreme case of the file cabinet analogy, the brain can register all motor commands and the following sensory outcome in a lookup table memorizing the past. This lookup table could be later used to predict the outcome of any motor command that was previously used. This kind of memory is a pure past representation; however it cannot be called a forward model, since it is not capable of predicting the consequence of motor commands which were never issued in the past. Once we allow interpolation or extrapolation based on this lookup table, we can call it a forward model, and then, at the same time, we start to address the future and not only the past. As we allow our lookup table to forget past events and count more on the statistics of the past rather than on specific events, we can no longer call it a lookup table and we give more and more weight to addressing the future.

On the other extreme, we can put a well-structured forward model with a few parameters. These are learned from past examples, and facilitate temporal extrapolation to the future. By mapping the ability of the motor system to adapt and testing hypotheses as to the structure of possible internal models, we can gradually map the way in which the motor system uses past experience in order to behave in the future.

10. Discussion

The biological system is characterized by redundancy in each and every level: there is more than one joint configuration for each location of the hand; there are many possible muscle activations which can generate the same torque in the joint; and there numerous possible neural activations which can bring the same muscle activation. The problem of redundancy, also known as the Bernstein problem, is extensively discussed in the literature [10, 13]. Redundancy is a virtue of the motor system, rather than a problem, and therefore the last question in this review is this: How does the brain exploit the virtue of redundancy? In many cases, the brain makes use of this virtue to obtain flexibility and reliability, rather than solves the problem of redundancy by selecting a single solution.

Redundancy means that the mapping of the controlled plant is many-to-one: therefore, the function of the plant is not invertible, questioning the meaning of inverse controller in Fig. 2(a). In order to address this question properly, I will take a short detour to address the limitations of the block diagram approach that was adapted in this review (Figs. 1(a), 2 and 3(b)) and discuss the extent to which they can describe a computational model and the kind of physiological data that can support or refute a theory presented by a block diagram.

It is important to note that the block diagrams in this paper just illustrate the verbal description. In order to use them as specific computational models, one needs to clearly state the coordinates of the inputs and outputs, and the specific mathematical functions of each block in the diagram and each learning algorithm. Moreover, specific predictions about neural recordings can be derived only when the physiological counterpart of the blocks and the measured signals in the block diagram are defined, while for specific behavioral predictions it is sufficient to define the physiological counterparts of the observed behavioral variables. Let us illustrate this for the block diagram in Fig. 1(a) describing the servo hypothesis for the reflex loop. Let us call the neural command u measured in units of pulse per second (PPS), the joint angle θ, measured in radians (rad), the muscle and arm function $f(u)$, and the muscle-spindle function $g(\theta, \gamma)$; then, one can write the model mathematically as

$$\theta = f(u) = f[\alpha + g(\theta, \gamma)]. \tag{10.1}$$

In the general case, one can consider the signals $u(t)$, and the arm and muscle-spindle as dynamic nonlinear time varying operators, $f[u(t), t]$, $g[\theta(t), \gamma(t), t]$. Moreover, the motor neurons dynamics could be described in more details than the simple

summation of two firing rates in Eq. (10.1), however, this would requires additional blocks in the block diagram. Here, we just illustrate the relation between block diagrams, mathematical equations and the related physiological signals, and for that purpose, let us consider the steady state, in which each level of firing rate of motor neuron is mapped to specific joint angle, and each joint angle is mapped to specific muscle spindle firing rate.

The simplest implementation of this model is selecting arm and muscle function determining the angle to be related to the muscle shortening, $f(u) = ku$, where k is a constant describing this linear relation with units of [rad/PPS]. Similarly, let us model the muscle spindle as a simple summation of the gamma activity with the muscle length which is in turn proportional to the joint angle. In the following equation, the constant, c, represents this proportion and unit transformation between joint angle and firing rates at the muscle spindle, relative to the gamma firing rate, and therefore its units are [PPS/rad].

$$\theta = -k\alpha - k(c\theta + \gamma), \tag{10.2}$$

$$\theta(1 + kc) = -k(\propto + \gamma). \tag{10.3}$$

This extremely simplified selection of operators can already predict the relation between the joint angle and the neural command; however, it does not address the system dynamics, or its nonlinearities. This can be addressed using the same block diagram, but with dynamic system in the form of mathematical model in each block. Linear dynamic systems can be described by the impulse response and the Laplace transform, as elegantly done by McRuer *et al.* [97]. Block diagrams can be also enhanced by being more specific, e.g., replacing the block titled muscle and joints with two blocks representing the muscle as the force generator that moves the joints. This possibility raises another problem with block diagrams: the blocks are unidirectional, whereas the force in the muscles does not only determine the angle, but it is also influenced by the joint angle. This should be very carefully examined, and in some cases, a solution to the problem is to replace the classical input/output formulation with a two-port system. A block diagram along with the exact mathematical function of each block can be refuted or supported using physiological data. For example, behavioral data of measured joint angles in a well defined task can be used to either support or refute specific models of the arm and the joint. In more sophisticated computational models (Figs. 2 and 3), one can formulate a hypothesis about the neural structure that implements each block, and test it by means of fMRI, or by direct recording of the neural activity. Note that the latter requires additional assumptions as to the nature of the neural code. This is another important open question in neuroscience, but it is out of the scope of this review. In summary of this detour, as any scientific hypothesis, a block diagram along with its proposed mathematical expressions can be either supported or refuted using physiological data, such as behavioral measurements, muscle activations, and neural signals.

Let us return to the issue of redundancy. Optimal control can be considered as a solution for the problem of redundancy, e.g., by minimizing the norm of the control signal, pseudo-inverse can be used to replace the inverse model block in a non-invertible redundant system (Fig. 2(a)). However, the real challenge, in my opinion, is to understand how the brain uses different solutions under different circumstances. Multiple internal models [56, 160] might be the key to represent multiple solutions to the same goal [73]. Nevertheless, the criteria for selecting one of the multiple solutions under various cases are open for future research.

According to Bernstein, redundancy is a key property unique to biological systems compared to artificial systems (of his time). Today, a few artificial systems employ redundancy and then exploit it, usually for robustness. However, there is still a vast potential in imitating technology to learn from the biological motor control system about exploiting the virtue of redundancy. Therefore, answering this question has wide scientific as well as technological and medical potential benefit.

Clearly, there are many open questions I failed to list. These include the use of robust control and other engineering approaches not yet adopted by the computational motor control community, and many other computational models developed to fit specific neural structures. Nevertheless, even with this short list of open questions, starting from Turing and ending with Bernstein, we have a lot of work before us as we strive to formulate a reasonable computational model for the motor system. At the same time, as described in this review, we have made significant progress during the last few decades, and start to see the fruits of these efforts in new upcoming technologies of brain machine interfaces and rehabilitation robotics.

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