

REVIEW | *Modularity and Compositionality in Motor Control: Acknowledging Emilio Bizzi*

From motor planning to execution: a sensorimotor loop perspective

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Submitted 20 November 2019; accepted in final form 20 September 2020

Bizzi E, Ajemian R. From motor planning to execution: a sensorimotor loop perspective. *J Neurophysiol* 124: 1815–1823, 2020. First published October 14, 2020; doi:10.1152/jn.00715.2019.—How is an evanescent wish to move translated into a concrete action? This simple question and puzzling miracle remains a focal point of motor systems neuroscience. Where does the difficulty lie? A great deal has been known about biomechanics for quite some time. More recently, there have been significant advances in our understanding of how the spinal system is organized into modules corresponding to spinal synergies, which are fixed patterns of multimuscle recruitment. But much less is known about how the supraspinal system recruits these synergies in the correct spatiotemporal pattern to effectively control movement. We argue that what makes the problem of supraspinal control so difficult is that it emerges as a result of multiple convergent and redundant sensorimotor loops. Because these loops are convergent, multiple modes of information are mixed before being sent to the spinal system; because they are redundant, information is overlapping such that a mechanism must exist to eliminate the redundancy before the signal is sent to the spinal system. Given these complex interactions, simple correlation analyses between movement variables and neural activity are likely to render a confusing and inconsistent picture. Here, we suggest that the perspective of sensorimotor loops might help in achieving a better systems-level understanding. Furthermore, state-of-the-art techniques in neurotechnology, such as optogenetics, appear to be well suited for investigating the problem of motor control at the level of loops.

basal ganglia; compositionality; modularity; sensorimotor loop; synergy

INTRODUCTION

In May of 2018, a group of investigators met at a minisymposium in Santa Fe, New Mexico to discuss a point of view on motor control that has been gaining considerable momentum over the last decade. This view, framed in terms of spinal cord modularity and behavioral compositionality, posits that diverse motor behaviors are constructed by linearly combining a small set of spinal muscle groupings or “synergies” with different timing and scaling factors (Bizzi et al. 2008). A major function of these synergies is to simplify the control of movements, a notoriously hard computational problem, transforming it from having to control many individual muscles to having to control a few motor building blocks. Considerable evidence has accrued suggesting that low-dimensional synergistic control at the level of the spinal cord may indeed be a general strategy utilized by the central nervous system (CNS) for many behaviors.

Most of the presentations at the minisymposium dealt with detailed anatomical and physiological properties of synergies, particularly with regard to the spinal cord intermediate zone, where groups of interneurons form the basis of muscle synergies (Caggiano et al. 2016; Takei et al. 2017). However, always lurking in the background of these discussions was the overarching question of control—specifically, even if spinal cord synergies constitute the motoric building blocks of vertebrates, how are these building blocks coordinated in time by the supraspinal system to generate goal-directed movements? Though beyond the scope of the minisymposium, this question, or some manifestation of it, tended to be the landing place of most speakers as they concluded their talks with a mention of future research directions.

In a recent article, we described the current state of the field in the following metaphorical terms: “we have some idea as to the intricate design of the puppet and the puppet strings, but we lack insight into the mind of the puppeteer” (Bizzi and Ajemian 2015). To some extent, the minisymposium only reinforced this impression. For quite some time, much has been known about

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limb biomechanics (the design of the puppet). The presentations themselves highlighted the surge of recent findings related to spinal synergies (the puppet strings). But to date, very little is known about the really hard problem—namely, how does the CNS pull the strings? Of course, many important questions still remain regarding the structure of synergies (what exactly defines a synergy, how are they determined through development, how are they influenced by motor skill learning, how are they altered by neurological trauma, etc.). In fact, many of the articles in this special issue address precisely these questions. But it at least appears as if the community of motor neuroscientists is converging around a loose consensus regarding the existence of synergies of some sort. In contrast, far more speculative and difficult to find are detailed proposals as to how, even assuming the existence of synergies, the CNS manages to generate effective control signals, a problem we refer to as the problem of supraspinal pattern formation.

In this brief essay, part commentary and part review, we provide no answer to this fundamental problem, nor do we attempt to survey existing proposals. Rather, we simply adopt the perspective of sensorimotor loops as a way to frame the problem of supraspinal pattern formation with respect to recent developments in the literature. By “perspective of sensorimotor loops” the following is meant: 1) synergies likely constitute the fundamental building blocks for movement control, and their patterned recruitment is largely dictated by the cortical output regions that give rise to the corticospinal tract; 2) there exist multiple sensorimotor loops involving the cortex, other brain regions, the spinal cord, and the sensorimotor periphery, all of which include these cortical output regions along their path; 3) each of these loops serves distinct, yet crucially overlapping, functional roles in solving the supraspinal pattern formation problem; 4) the continuous convergence of these loop activities at the cortical output regions engenders the emergence of functionally appropriate movement commands by shaping both loop activity and motor output activity; and 5) the mathematical perspective from which to view this phenomenon is that of distributed representation and distributed control in a complex multiscale system (Kitano 2004).

We begin the discussion by focusing on the role of cortical preparatory activity in primary (M1) and premotor motor (PMd) cortices as a way to set the stage for pattern formation. Next, we briefly discuss some of the sensorimotor loops that connect the cells in the motor cortices with many CNS areas such as the basal ganglia, cerebellum, thalamus, parietal cortex, and sensory areas. Finally, we close with a discussion of the dual role of spinal synergies—that is, not only are they activated via supraspinal sensorimotor loops but at the same time they also participate in sensorimotor loops that include peripheral feedback to the supraspinal centers and, through this reentrance, help shape their own activation commands. Again, our aim is not to describe a theory for the function of these sensorimotor loops or how they interact but rather to frame recent results and current understandings from that perspective.

PREPARATORY NEURAL ACTIVITY: SHIFT TO A DYNAMICAL APPROACH

The initial critical step—the wish to move and the concomitant appearance of neural activity in a number of cortical and subcortical areas—has been a topic of much speculation. The

process was succinctly expressed by Roger Sperry: ideas generate cell activity (Edelman 2004). Indeed, there is ample evidence that “idea-evoked processes” activate neurons in numerous cortical areas before movement’s initiation (Allen et al. 2017; Steinmetz et al. 2019). Surprisingly, these cortical cells may become active even when subjects merely think about performing an action and when subjects observe others performing the same movements (Jeannerod 2001).

The broad distribution of preparatory cells over the cortex is not surprising—after all, even a simple movement is a global body event. Besides activating the muscles involved in moving a body limb, the motor system must anticipate and cope with a spectrum of movement-related challenges including the concurrent postural adjustments necessary to achieve stability, the inhibition required to turn down activity in antagonistic muscles, the setting of the appropriate gains in afferent sensory fibers, and the processing of corollary discharge signals.

The main tool for studying preparatory activity has been and remains the delay movement task, in which an initial cue specifies the type of movement to be performed but movement initiation is delayed for a variable length of time until a “go” cue comes on. Eliciting activity in such a task is easy, but interpreting what it means is more problematic. This activity could reflect a number of things, including a primed version of the neuron’s movement-related response, an inhibitory response designed to facilitate subsequent movement release, or a specific preparatory function that is distinct from its movement-related function. Initial attempts to settle this question used the representational approach to encoding developed by Evarts (1968), in which investigators recorded from single cells and established the level of correlation between neural activity and individual movement parameters. These efforts tended to suggest that a cell’s preferred direction in the delay period seemed to be correlated with its movement-related preferred direction, suggesting perhaps some sort of priming (Georgopoulos et al. 1982; Sergio and Kalaska 1998).

However, the shortcomings of the representational approach became well known over time. Specifically, it is hard to know whether a correlation is real or artifactual when movement variables both vary over time and are themselves interrelated in an orderly fashion through the equations of motion (Ajemian et al. 2008; Churchland and Shenoy 2007; Fetz 1992; Scott 2008).

On the basis of these findings, investigators questioned the idea that motor cortical neurons possess fixed preferred movement parameters. For instance, Hatsopoulos and Amit (2012) showed that neurons switch movement parameters during the course of actions, and Crammond and Kalaska (2000) showed that individual neurons do not have consistent relationships with movement direction over hundreds of milliseconds.

Over the last two decades, the paradigm has shifted because investigators are able to record simultaneously from dozens of neurons with chronically implanted recording arrays and because state-space methods have been developed to analyze this type of data (Churchland et al. 2012; Yuste 2015). In these methods, which take advantage of the fact that movement emerges from the simultaneous activity of a large ensemble of neurons, activity is depicted in a high-dimensional space whereby each axis represents the firing rate of one neuron. To make sense of the resulting high-dimensional data, various methods for dimensionality reduction are applied. Finally, the recorded neurons are linked through dynamics, so that the evolution of the system state through time

is what carries meaning. With these methods, new insights have arisen into the possible role of preparatory activity (Li et al. 2016).

For example, two recent papers employing this type of approach provide evidence that preparatory activity is far from being an early indicator of movement-related activity and, instead, reflects a separate but facilitating computation. Elsayed et al. (2016) showed that at the population level preparatory and movement activity occupy orthogonal subspaces, although a simple transformation relates the two, suggesting that preparatory activity is crucial for putting the system in a state that enables the dynamic evolution of movement commands. Lara et al. (2018) showed that a relatively brief period of dynamical preparatory activity appears to precede movement activity across tasks regardless of whether there is a delay, suggesting that these dynamics appear to be a necessary part of the overall sensorimotor computation. Similar results were obtained in Michaels et al. (2018) and Churchland et al. (2006).

Although the dynamical systems approach has, in certain respects, been an improvement over the representational approach in understanding the role of preparatory activity, it too has shortcomings: dimensional reduction techniques make the relevant “variables” difficult to interpret and inconsistent from one study to the next; recording from dozens of neurons simultaneously is an improvement over recording from a single neuron but still falls orders of magnitude short of the number of neurons involved; and, in contrast to a feedback view of movement, the dynamical systems approach generally suggests that once a movement is prepared, motor cortical dynamics alone govern how movement dynamics unfold (Kalaska 2019). Regarding this last point, a recent paper, Sauerbrey et al. (2020), suggests that a continuous flow of external inputs to the motor cortex is critical to making movements above and beyond intrinsic cortical dynamics.

THE CENTRAL ROLE OF CORTICAL LOOPS

The cortical loops provide reciprocal connections between frontal motor cortical cells and the basal ganglia, cerebellum, thalamus, parietal cortex, and the brain stem. The signals conveyed by these loops contribute to the formation of spatiotemporal patterns of activity for the spinal cord. What follows is a brief description of the major loops.

CORTICO-CORTICAL LOOPS: FRONTO-PARIETAL

Direct anatomical connections between PMd and the parietal cortex and the dorsal premotor area have been shown by Pandya and Kuypers (1969) in monkeys. This multifunctional loop has been thought of as integrating multiple modalities of sensorimotor information, such as gaze direction and limb proprioception, to make the coordinate computations necessary for accurate reaching (Wise and Kurata 1989). This circuit, in conjunction with prefrontal and cingulate cortex, is also involved in the selection of alternative actions (Pesaran et al. 2008; Rathelot et al. 2017). The anterior intraparietal cortex and ventral premotor area are part of a network linked to hand grasping movements (Lehmann and Scherberger 2013).

In a recent study using the state-space methods, Michaels et al. (2018) recorded neurons from ventral premotor cortex and the anterior intraparietal region in monkeys. The animals made reach-to-grasp movements after varying amounts of preparation time. The data recorded during grasping showed that the initial

neural trajectory for all delays (0–300 ms) was similar for the same movement, indicating that this activity is critical for movement selection, generally consistent with, though expanding upon, earlier interpretations.

CORTICO-THALAMIC-LOOP

There are at least three loops connecting the motor cortex with the thalamus.

- 1) A contingent of cells from layer 5 of the motor cortex projects to regions of the thalamus that project back to the motor cortex. This pattern of a cortical region projecting to the parts of the thalamus that project to it is a familiar but poorly understood motif that pertains to many regions of the cortex. This particular cortico-thalamic-cortico loop may make it possible to maintain activity in the motor cortical cells during the delay period (Economo et al. 2018).
- 2) A functionally similar frontal-thalamic-cortical loop was described in the mouse. Neurons in the anterior lateral motor cortex (ALM) project to parts of the thalamus and then back to ALM (Guo et al. 2018). Note that the ALM-thalamus loop is segregated from the M1-thalamic loop (Guo et al. 2017).
- 3) There is also a thalamic loop that goes through the cerebellum as well. This loop is discussed further below, and it, like the M1-thalamic loop, may be involved in the process of maintaining the activity of M1 neurons during the delay period (Gao et al. 2018).

CORTICO-STRIATAL LOOP

The cortico-striatal projections are made up by cells originating from different cortical centers and different cortical layers (Shepherd 2013). Alexander et al. (1986) identified five cortico-basal ganglia circuits (designated “motor circuit,” “oculomotor,” “dorso lateral prefrontal,” “lateral orbito frontal,” and “anterior cingulate”). Each pathway conveys outputs from distinct cortical areas and connects to different regions of the striatum. The functional diversity of the cortico-basal ganglia circuits stems from the diverse cortical areas involved. The basal ganglia are involved in many cognitive-motor functions such as habit formation (Graybiel 2008) and the encoding and recoding of procedural memory (Barnes et al. 2005). Here, we focus exclusively on the “motor circuit,” which receives projections from M1, from somatosensory areas, from areas 5 and 6, as well as from supplementary motor area (SMA).

On the output side the putamen sends topographically organized projections to substantia nigra pars reticulata via a monosynaptic GABAergic pathway from D1 medium spiny neurons that provides modulation of movement strength (Shadmehr and Ahmed 2020). Another pathway from D2 medium spiny neurons projects to the globus pallidus and subthalamic nucleus. Coordinated activity happens in both pathways, and this activity leads to parsing and concatenation (Jin et al. 2014). According to Hoover and Strick (1993), the output nuclei of the basal ganglia project, via the internal segment of the globus pallidus, to three cortical areas: the primary motor cortex, the SMA, and the ventral premotor area.

Two important papers have recently contributed to our understanding of the processes that are taking place in the basal ganglia. Markowitz et al. (2018) and Wiltshchko et al. (2015) used a confluence of machine learning techniques to detect a finite library of submovements represented in the

basal ganglia of freely moving mice. These submovements embody recurring behavioral modules or motifs that exist at the subsecond timescale (350 ms), a scale sufficient to act as building blocks for volitional movements that occur on the scale of seconds. In essence, one can think of these modules as a kind of micro-pattern generators representing recognizable action segments.

Because of behavioral constraints, when one submovement arrives at the putamen it is not equally likely to be followed by any other submovement—rather, just as in an alphabet there exist preferred combinations of letters, stereotypic groupings of these submovements lead to functional movement chunks. This process of concatenation may lead to the formation of full movements and movement sequences. When new behaviors are expressed, new combinations of modules are observed simply by reusing the same modules without forming any new ones. As a cautionary note, rodent studies like these do not involve EMG recordings from a wide selection of both posture-related and movement-related muscles. Since muscle activity serves as the “ground truth” for the motor system’s intended state, it is difficult to know whether the apparent kinematic chunking is likewise reflected in the composite muscle commands.

In summary, the basal ganglia have been proposed to be involved in a variety of cognitive functions as well as in organizing motor actions into chunks and segmentation. Chunking facilitates movement production by combining motor elements into integrated units of behavior (Graybiel 1998, 2008).

CORTICO-CEREBELLAR LOOPS

For a brief glance at cerebello-cortical connections, we will 1) describe the anatomical closed-loop circuit between M1 and specific areas of the cerebellar cortex (Hoover and Strick 1999) and 2) discuss a recent study showing that patients affected by cerebellar ataxia display disrupted muscle synergies.

Kelly and Strick (2003) investigated the cortico-cerebellar loop by utilizing two types of viruses. With retrograde transneuronal transport of rabies viruses, they showed that Purkinje cells located in lobuli 4 and 6 of the cerebellar cortex project to the arm area of primary motor cortex (M1). With anterograde transneuronal transport of herpes simplex virus, they showed that neurons in the arm area of M1 project via the pons to the Purkinje lobuli 4 and 6. The results indicate a closed-loop structure as a fundamental feature of cortico-cerebellar interactions.

In a recent paper, muscle synergies were recorded from patients affected by cerebellar ataxia (Berger et al. 2020). The results indicated that, relative to a control group of healthy subjects, cerebellar damage disrupted in patients the temporal patterning by which synergies were recruited but left largely intact their underlying spatial structure. On the basis of these results, the authors speculate that the cortico-cerebellar loop is crucial to the temporal component of the supraspinal pattern formation problem, whereas the motor cortical areas are more likely involved with directly determining the spatial structure of synergies. This speculation is consistent with a long history of work implicating the cerebellum in timing problems (Ivry and Keele 1989). Regardless, these results demonstrate the importance of this loop and highlight the need to record simultaneously from afferent and efferent branches to better elucidate its role.

WHERE THE LOOPS END UP: CONVERGENCE UPON M1 AND PMD CELLS

Areas M1 and PMd are, to a great degree, the common focal point of convergence for loop-driven activity across many areas of the central and peripheral motor systems. Signals from cerebellum, basal ganglia, thalamus, and sensory cortical areas converge upon the diverse types of neurons of M1 and PMd, as well as SMA, cingulate motor area, and a portion of area 5 (Rathelot and Strick 2006, 2009). Ultimately, the convergence of these inputs mobilizes the pyramidal tract neurons of areas M1, PMd, and the other tract constituents into forming time-varying control signals sent to spinal cord interneurons and motoneurons. How these inputs work together and interact with a vast number of rapidly changing external signals generated during body movements is still a deep and open question.

In the absence of a global theory of sensorimotor loop coordination, investigators have naturally tended to focus instead on understanding what the neurons in these regions are “encoding.” Hence, there has been a focus on the representational approach, in which individual neurons are assumed to encode movement variables, and there has been a more recent focus on the dynamical systems approach, in which a group of recorded neurons dynamically interact to generate a functional spatiotemporal command (Shenoy et al. 2013). Two other “encoding” approaches envisioned as taking place at the trajectory level need mention. Aflalo and Graziano (2006) showed how external inputs form stereotypic and behaviorally relevant short trajectories of ~300- to 400-ms duration. This segmentation is somewhat reminiscent of that which Wiltchko et al. (2015) identified in the mouse putamen—that is, the presence of submovements at the subsecond timescale (350 ms) that were concatenated by cortico-striatal signals. Hatsopoulos and Amit (2012) put forward a model in which they argue that a wide range of subtrajectories or movement fragments are represented in M1. These segments are thought to be controlled by the different classes of motor cortical cells.

Ultimately, if motor control is implemented by multiple, redundant, and distributed sensorimotor loops, it is very difficult for any approach to disentangle real correlations from artifact without a thorough understanding of how each of those loops contributes functionally to movement control. Indeed, two recent investigations with rodents suggest that overall movement coordination—that is, the coordination of multiple movements in sequence involving different body parts on the timescale of seconds—is accomplished via sensorimotor loops spread throughout the brain. Stringer et al. (2019) and Musall et al. (2019) found that cognitive, sensory, and motor information were not confined to specifically designated cortical regions but were instead thoroughly intermixed across regions. As a consequence of combining multimodal information, diverse cortical patches of integrated activity were formed on the cortex and subcortex. These scattered sensory-motor patches may have a useful function because brain location might create a specific functional identity for these microcircuits to be utilized in sensory-motor coordination. Although it is more difficult to record in nonhuman primates during the performance of sequential whole body behaviors, two studies do show an analogous multimodal mixing of task-related information in the primate brain (Engel et al. 2015; Ruff and Cohen 2014).

What would be desirable, rather than recording blindly from areas in which multiple sensorimotor loops converge potentially

at different cortical depths, would be an approach that can tease apart the spatial and layer targets of the different loops, both at the point of convergence and throughout the CNS. Though inconceivable a few years ago, these types of investigations are now possible thanks to optogenetic technology that enables targeted interference in cortical circuits through stimulation or inhibition of different classes of neurons such as those in layers 2, 3, and 5 (Sauerbrei et al. 2020). A thorough understanding of the function of the many sensorimotor loops is essential if we want to understand the deep problem of supraspinal pattern formation. In what follows, we have outlined at the conceptual level potential experiments of this type on two important feedback loops: the cortico-striatal loop and the cortico-cerebellar loop.

Neural activity in the putamen and cerebellum appears to follow the onset of neural activity in the cortical motor areas. This finding possibly suggests that the basal ganglia and cerebellum receive something akin to an efference copy from M1 and PMd. By simultaneous recording at multiple loop locations from the fibers that make up these loops, we may obtain some needed perspective on what is transmitted to the cortex from striatum and cerebellum during different behaviors.

Along similar lines, we could see reasons for recording from the fibers of a loop involving a pathway originating in PMd and connecting with interneurons that set up the muscle synergies. During movements, the muscle synergies together with their muscle spindles and joint and skin receptors generate a flow of diverse sensory signals that, by way of multiple ascending pathways, provide M1 and PMd cells with the information necessary to adapt to the vagaries of the external world. Thus, recording simultaneously from the descending cortico-spinal fibers and the ascending spino-cortical fibers might open up new vistas on the problem of supraspinal pattern formation. Specifically, the sensory information including its timing and structure might provide a kind of a scaffolding that contributes to the formation of spatiotemporal patterns.

The investigative strategy on feedback loops described here rests on the assumption that the formation of spatiotemporal patterns may be best understood by focusing on individual feedback circuits. Clearly, this strategy has limitations because it neglects local dynamic interactions. Nonetheless, an understanding of loop function enables principled simulations of movement control robustness in line with robustness analyses for other biological complex systems (Kitano 2004); such simulations are specifically designed to identify real versus spurious correlations, a problem that has plagued the field of motor neurophysiology since its inception. Furthermore, given that movement control appears to be a brainwide function and that these loops embody the evolvable elements of the motor control system, they may indeed represent the most natural way to decompose the system (Sauerbrei et al. 2020). We advocate this strategy as the most effective way for the field to make progress moving forward.

CORTICO-SPINAL PATHWAY

The convergence of a complex pattern of reciprocal connections among motor cortical areas shapes the functional activities of the descending cortico-spinal tract, which originate from the primary motor cortex, PMd, SMA, cingulate motor areas, and parts of area 5 (Dum and Strick 1991).

Rathelot and Strick (2006), in a series of remarkable papers, revealed a number of anatomical features of these corticospinal tracts. By utilizing the techniques of retrograde transport of the rabies virus, they examined the cortico-motoneuronal (CM) cells that make monosynaptic connections with the motoneurons of monkeys' finger muscles and found that CM cells relating to a single finger muscle are widely distributed across M1 arm and shoulder areas. Interestingly, there was no evidence for focal representation of single muscles in M1.

In a subsequent publication, Rathelot and Strick (2009) revealed another unsuspected feature of M1 anatomy. They found that M1 has two subdivisions—from the caudal part of M1 neurons make monosynaptic contacts with motoneurons, and, in contrast, the fibers from the rostral portion activate motoneurons indirectly via the spinal cord interneurons.

SPINAL CORD MODULARITY: THE KEY ROLE OF MUSCLE SYNERGIES

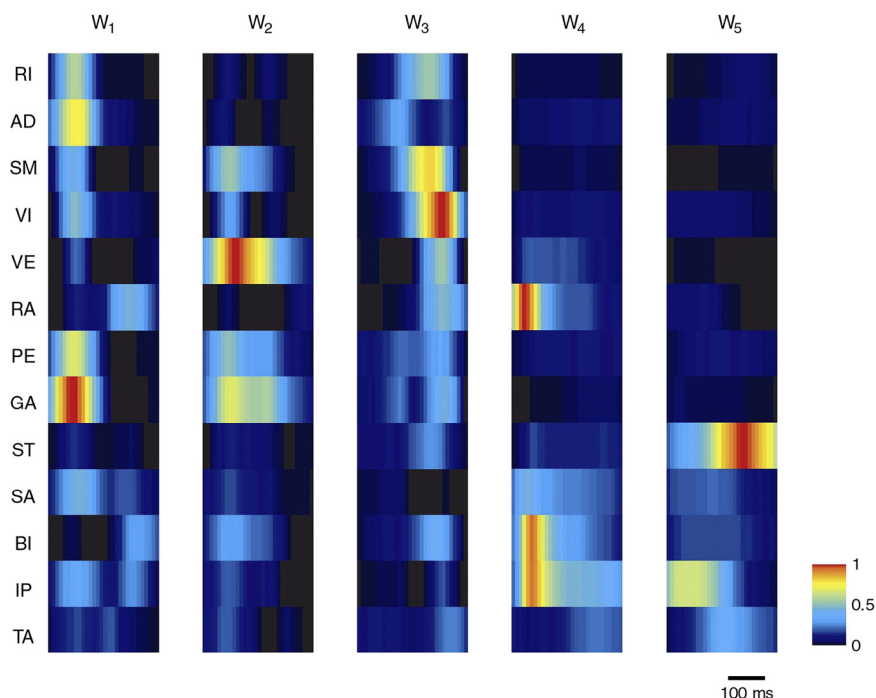
Recent investigations have shown that in the spinal cord intermediate zone there are modules made up of groups of spinal interneurons (Caggiano et al. 2016; Hart and Giszter 2004; Saltiel et al. 2001; Tresch et al. 1999). These studies have demonstrated that a spinal module is a functional unit that generates a specific motor output by imposing a specific pattern of muscle activations (muscle synergies) (Bizzi et al. 1991). Muscle synergies are, presumably, neural coordinative structures that function to alleviate the computational burden associated with the control of movement and posture (Ting and Macpherson 2005).

Anatomically, the modules are made up of groups of spinal interneurons whose efferent fibers contact a distinct set of motor neurons (Takei et al. 2017). It follows that whenever these interneurons are activated by descending corticospinal impulses and/or reflex pathways from the periphery, the corresponding muscle synergies become active. This process leads to the utilization of muscle “synergies” as a type of functional building block, which in combination, leads to the “construction” of voluntary movements (Bizzi et al. 2008; Cheung et al. 2005; d'Avella et al. 2003; d'Avella and Bizzi 2005). From an empirical standpoint, a factorization algorithm that takes as input all the recorded muscle EMG data is utilized to extract muscle synergies and activation coefficients. The factorization procedure essentially performs a dimensionality reduction by grouping muscles that tend to covary in the data set into synergies. (Fig. 1).

In the last few years, many investigators have examined motor behaviors in humans (Ivanenko et al. 2004) and animals (Krouchev et al. 2006). The results show that combining a small set of muscle synergies appears to be a general strategy that the central nervous system utilizes for simplifying the control of movements (Fig. 2).

All in all, the following important points have emerged from spinal cord investigations: 1) the same synergy may be utilized in different motor behaviors; 2) different behaviors may be constructed by linearly combining the same synergies with different timing and scaling factors; 3) the development of new skills over long periods of time leads to the formation of new specialized task synergies; and 4) recent investigations of stepping patterns in neonates and toddlers as well as rats demonstrate that motor synergies are present at birth and retained during development (Dominici et al. 2011). Similar observations made with 5

Fig. 1. Time-varying muscle synergies extracted from jumping, swimming, and walking muscle patterns in three frogs. Each synergy (columns W_1 – W_5) represents the activation time course (in color code) of 13 muscles over 30 samples (300-ms total duration) normalized to the maximum sample of each muscle. AD, adductor magnus; BI, biceps; GA, gastrocnemius; IP, ilio-psoas; PE, the ankle extensors peroneus; RA, rectus anterior; RI, rectus internus; SA, semitendinosus; SM, semimembranosus; ST, mainly semitendinosus; TA, tibialis anterior; VE, vastus externus; VI, the knee extensor vastus internus. Reprinted with permission from Bizzi et al. (2008).

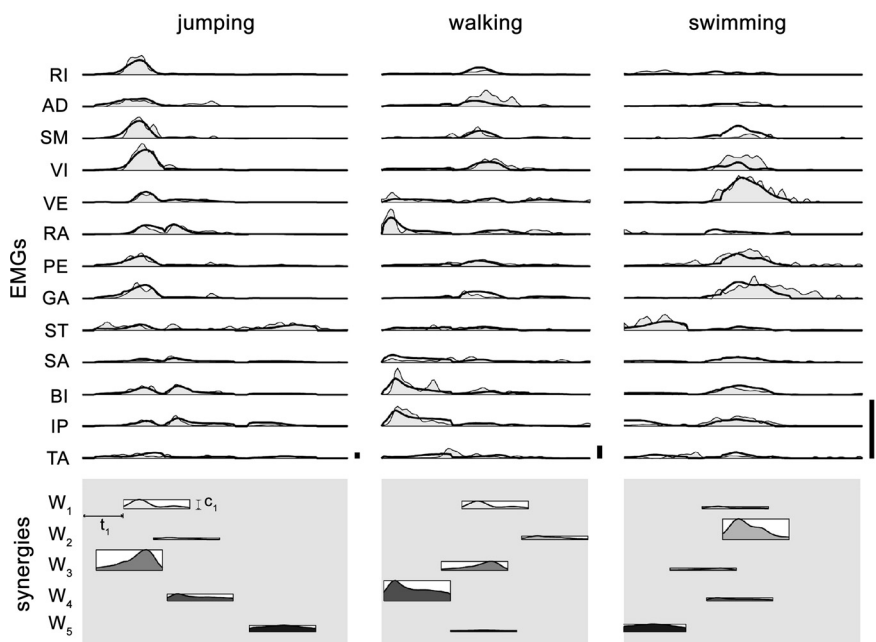


days postnatal rodents demonstrated that muscle synergies remained largely unaltered during subsequent development (Yang et al. 2019).

Taken together, the evidence suggests that the spinal cord operates as a discrete system of modules whose combinatorial control by upstream structures generates functional movement commands. In a way, the motor system is thus like a language, a system with discrete elements and a set of rules for combining them to generate a large number of meaningful entities distinct from the elements themselves. And just as with language, the combinatorial system can be extended to accommodate different levels of expertise.

At this point we do not have a mechanistic understanding as to how the supraspinal loops, possibly in conjunction with mid-brain circuits, generate a series of commands that involve the selection of spinal synergies with their different timing and scaling factors. In this regard, it is worth mentioning an observation by Overduin et al. (2012) that in monkeys cortical microstimulation evoked, in a few instances, muscle synergies similar to those generated by the same animal's voluntary movements. Clearly, this preliminary observation needs to be taken up, particularly in view of the recent advances in the areas of anatomy and physiology that are now providing an array of new tools for attacking this type of complex problem.

Fig. 2. Examples of reconstruction of EMG patterns as combinations of time-varying muscle synergies. Shown are examples of a jump, a walking cycle, and a swimming cycle. *Top* (EMGs): the thick line shows the reconstruction of muscle patterns, and the shaded area represents the rectified, filtered, and integrated EMGs. *Bottom* (synergies): the coefficients of the 5 synergies as the horizontal position (onset delay, t_i) and the height (amplitude, c_i) of a rectangle whose width corresponds to the synergy duration. The shaded profile in each rectangle illustrates the averaged time course of the muscle activation waveforms of the corresponding synergy. Different amplitude scaling is used in the 3 columns. Note that same synergies are found to contribute to different movements. Synergies W_1 , W_3 , and W_4 are a constituent of both jumping and walking, but with different coefficients of activation of EMGs. Synergy W_5 is used in both jumping and swimming. It follows that different behaviors may be constructed by linearly combining the same synergies with different timing and scaling factors. Reprinted with permission from Bizzi et al. (2008).



In summary, recent spinal cord investigations have added novel perspective on spinal cord mechanisms by demonstrating a previously unsuspected way to generate movements based on modularity and compositionality.

CONSIDERATIONS ON INTEGRATING THE PATHWAYS

The core question in motor control—what we call the problem of supraspinal pattern formation—is how the supraspinal system generates, across time, functional control signals. In the context of the synergy hypothesis, the question refers to how synergies in the spinal cord are correctly recruited. As stated up front, we have no answer to this imposing question. Instead, we briefly discuss two reasons why the sensorimotor loop perspective described above constitutes, in our opinion, the most effective way forward for the field, particularly as contrasted with the representational approach or the state-space dynamics approach.

The Ubiquity of Feedback

Whether one considers the CNS in general or the motor system in particular, feedback is everywhere. With few exceptions, a brain region that projects prominently to another brain region invariably receives significant feedback projections. In the motor system, the prominent role of feedback extends even more noticeably to the periphery, where most major nerves carry 5–10 times as many afferent fibers as efferent ones (Anand et al. 2017). Although pure feedforward control serves an important role in robotics, it has little place in biological motor control, where behavior arises more organically as a balancing act based on the continuous interplay between system inputs/outputs and behavioral predictions/realizations (Musall et al. 2019; Sauerbrei et al. 2020; Stringer et al. 2019). A variety of factors likely explain the centrality of feedback in biological motor control, including the intrinsic noisiness of the system components (Ajemian et al. 2013) and the functional need for the simultaneous feedback of position, velocity, and force information when modulating end-effector impedance (McIntyre and Bizzi 1993), a key aspect of biological motor control infrequently emulated in robotics. The important point for our purposes is that a sensorimotor loop perspective automatically forces one to take feedback into consideration, because one is required to hypothesize the type of information and transformations occurring within each loop. Neither the representational approach nor the state-space dynamics approach can easily integrate feedback, since information tends to be considered in isolation in specific regions.

The Theoretical and Experimental Evaluation of Robustness

A hallmark of all complex biological systems—a category to which the motor system certainly belongs—is biological robustness (Kitano 2004), meaning that they are equipped with emergent compensatory mechanisms to enable acceptable performance in the face of multiple possible perturbations. For the motor system, potential perturbations include a large burst of motor noise, temporary malfunction in a specific pathway, actuator miscalibration as a result of fatigue, etc. The sensorimotor loop perspective lends itself to a rigorous evaluation of robustness through computer simulation, since a concrete mathematical role must be proposed for each loop included in the model (e.g., the cerebellum embodies an expansion recoder perceptron that provides continuous adjustments to

motor output based on the current inflow of system state (Albus 1971; Marr 1969). Of course, these hypotheses are likely wrong—or at least oversimplifications—but they enable construction of a well-defined test bed for further model iteration and improvement. More specifically, such a model allows testing of 1) the compensatory response of the overall circuit to specific perturbations (such as “lesioning” a loop) and 2) the robustness of this response to variations in system parameters. The field of optogenetics makes possible manipulations of specific circuits as a means of generating the type of loop-oriented data against which model predictions can be compared. Although the use of optogenetic techniques has been restricted mostly to rodents, ongoing efforts seek to extend the domain of application to nonhuman primates. For our purposes, neither the representational approach nor the state-space dynamics approach is particularly amenable to this kind of systematic falsification, since they arise computationally as post hoc data-analytic techniques, rooted largely in correlation and dimensionality reduction.

CONCLUSION

Our ability to move effortlessly belies the extraordinary computational burden therein entailed. How this happens across the animal kingdom remains a miracle and a mystery.

We focused on the loop architecture of the biological movement system, because we believe that a lot more is known about the puppet and the strings than the mind of the puppeteer—indeed, given the presence of loops, there exists no single controlling authority but rather a highly distributed emergent control scheme about which we currently know little. To understand how this system works, many have used the representational approach in the past and are more recently applying a dynamical systems approach. But these approaches are both fundamentally correlational, and in a highly distributed system teasing apart meaningful correlations and artifact is a difficult, almost intractable challenge. So perhaps instead it makes sense to take a loop perspective on investigating the sensorimotor system, especially since current tools like optogenetics are ideally suited to this approach. Should loop functions eventually be known, mathematical modeling can ultimately simulate the local flow of neural activity.

Of course, the problem of sensorimotor control is even more difficult than we suggest, as we deliberately avoided dealing with a number of interesting and important issues. To name just a few, we have not dealt either with motor learning or motor generalization. Another interesting question concerns the neural substrate of routine habitual movements versus new and unusual actions. Furthermore, there are other loops in the system that we did not mention, including the mesencephalic motor system.

But however difficult the problem is, it is also fascinating and important. Nature needed millions of years to achieve the sublime level of performance of a tennis player or a gymnast, a level of adroitness that far surpasses state-of-the-art robotics capabilities. Somehow, nature has generated a system that, with variations (a cerebral cortex is not present in all vertebrates), works for the entire universe of species. If we are ever able to gain a complete understanding of this biological machinery, clinical neurology and the field of rehabilitation will benefit, and the engineers might be able to improve their devices.

ACKNOWLEDGMENTS

The authors thank Charlotte Potak for assistance with preparation of the manuscript for publication.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

E.B. and R.A. conceived and designed research; R.A. interpreted results of experiments; E.B. and R.A. prepared figures; E.B. and R.A. drafted manuscript; R.A. edited and revised manuscript; E.B. and R.A. approved final version of manuscript.

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