

# Motor systems

## Editorial overview

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### Abbreviations

<b>ACh</b>	acetylcholine
<b>AMPA</b>	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
<b>CPG</b>	central pattern generator
<b>DA</b>	dopamine
<b>DUM</b>	dorsal unpaired median (neuron)
<b>GABA</b>	$\gamma$ -aminobutyric acid
<b>GM</b>	general movement
<b>NMDA</b>	<i>N</i> -methyl-D-aspartate
<b>PPN</b>	pedunculo-pontine nucleus
<b>SC</b>	superior colliculus
<b>SK</b>	slow potassium (current)
<b>SNc</b>	substantia nigra, pars compacta
<b>STN</b>	subthalamic nucleus

### Introduction

This collection of reviews concerning the neural control of the motor system is published at the end of the 20th century. One could argue, from an historical point of view, that the past one hundred years have been the century of the neuron. During this time, investigators from many countries have thoroughly characterized both the morphology and the physiology of the neuron. Major discoveries about the properties of neurons, made in the early years of this century, have led to the gradual emergence of the concept of neural networks such as central pattern generators (CPGs). These pattern generators have been described in great detail, particularly in invertebrates and in lower vertebrate preparations. What is remarkable is that the motoric functions of some of these pattern generators, such as Grillner's 'fictive motor pattern' (pp 663–669) can now be explained in terms of activation of ion channels and receptors — a feat that until recently was deemed unlikely.

Bridging the gap from ion channels to networks and behaviour is now possible, as demonstrated by the work of Grillner and other investigators. The development of new molecular and cellular techniques, such as multicellular recording *in vivo* and new powerful imaging approaches, have made it possible to envisage the emergence of comprehensive mechanistic explanations linking neurobiology with behavior.

### Neural network organization: from cellular properties to cognition

During the 1960s and 1970s, CPGs were considered to be structures capable of producing automatic and stereotyped patterns. In contrast, more recent investigations have demonstrated that the pattern generators can flexibly adapt to the conditions of the environment and various motor tasks. This is particularly true if we consider firstly the development of these networks, secondly the role of the neuromodulators and thirdly, at a more complex level, their relations with behavioural or cognitive tasks.

### Development of neural networks

In his review, Grillner describes various different electrophysiological preparations and compares their different values as experimental tools. His goal is to contrast the functional properties of networks in the embryo or the larval stages with the networks found in the fully developed, adult organism. He considers different examples, mainly in vertebrates, but focuses on two important preparations: the mouse respiratory network and the neonatal rat locomotor network. In both these systems, the properties of ion channels and of different receptors show signs of immaturity. For instance, at day 0, GABA<sub>A</sub> induces a depolarisation that depends on the Cl<sup>-</sup> equilibrium potential, but only a few days later, the classical inhibitory effect of GABA<sub>A</sub> is manifest. Similarly, NMDA receptors are over-expressed during the first week after birth, while AMPA receptors become functional a few days later. In the neonatal rat hippocampus, Ben Ari *et al.* [1] described a 'ménage à trois' between GABA, NMDA and AMPA: initially, GABA<sub>A</sub> and NMDA act in synergy to mediate an excitatory drive; only later do NMDA and AMPA become excitatory, while GABA<sub>A</sub> takes on its inhibitory role.

With respect to the adult locomotor circuit models, Grillner reports that — as opposed to the lamprey and mudpuppy *in vitro* preparations — we have not yet found an adult mammalian preparation in which the pattern generator can be described at the cellular level.

Another fruitful approach for understanding the development of pattern generators is to consider their genetic control. Bate (pp 670–675) makes a very interesting comparison between different embryonic circuitries; in particular, he describes the development of swimming in the *Xenopus* embryo and in the zebrafish, as well as the complex interactions existing between genetic and environmental factors. The implementation of genetic mutations in these model systems would make it possible to understand how different controls are exerted during locomotion.

With regard to opportunities for future studies, the zebrafish model seems to be very promising. The transparency of the

zebrafish provides a number of advantages, such as the identification of neurons, the imaging of neural activity and, most importantly, the opportunity for laser ablation of identified cells.

In addition, Bate raises the important and fascinating issue of the development of embryonic movements. This topic has been reviewed three times this year [2–4]. While it remains to be ascertained whether embryonic movements in regions as far apart as the retina, the hippocampus and the spinal cord have something in common, it is of interest that these movements are correlated with intracellular  $\text{Ca}^{2+}$  oscillations. These oscillations, in turn, may regulate gene expression as well as different neuronal functions during development, such as neurite extension, growth cone pathfinding and neuronal migration.

In the spinal cord of the chick embryo, random spontaneous activity can be detected in ventral roots before the axons of the motor neurons reach their muscle targets. During the early stages of development (up to stage 24), there is synchronous activity in both extensors and flexors; however, later, when GABA is present, reciprocal activation of flexors and extensors appears. Remarkably, in this preparation, there are also changes in excitatory neurotransmission: acetylcholine (ACh) drives the bursts at stages 25–28, but by stage 32, shortly after contact with muscle targets, glutamate takes over. Similar changes affect the developing locomotor circuits of the embryonic rat spinal cord, but glycine seems to be the most important neurotransmitter. Bate discusses the relations of these primitive rhythmic discharges with patterned motor activities.

It is interesting to relate the data on foetal and neonatal movements discussed by Bate with those reviewed by Forssberg (pp 676–682). The most frequent movement patterns of the human foetus and newborn infant are ‘general movements’ (GMs), which involve all parts of the body and are performed at variable speeds and amplitudes. The quality of these GMs are useful for predicting the later development of cerebral palsy. Abnormal movement patterns are strongly associated with lesions of the immature brain.

### Neuromodulation and neural networks

Pflüger (pp 683–689) reviews the concept of neuromodulation, both during development and in the fully mature nervous system. He argues that modulatory neurons cause long-lasting changes of the synaptic connections within networks. These changes may serve to reconfigure the network and hence produce different output patterns. Examples of reconfiguration have been described in the stomatogastric system and the spinal locomotor network of *Xenopus*. In adult crustacea, for instance, the gastric and pyloric rhythms are different, but in the embryo there is only one rhythm. Conceivably, specific neuromodulatory fibres in the embryo may prevent the normal expression of the adult-like pattern.

The spinal locomotor network of the *Xenopus* embryo is a popular model system used by many investigators, including Grillner, Bate and Pflüger. In particular, Pflüger stresses the roles of two substances that act in opposition: serotonin (5-HT) and noradrenaline (NA). 5-HT is capable not only of changing the firing properties of the spinal motor neurons, but also of increasing the frequency of the larval swimming pattern; in contrast, NA slows down this frequency.

In the remainder of his review, Pflüger focuses on an interesting case in insects where a neuromodulatory system has been clearly identified. This system is composed of octopaminergic neurons (ventral/dorsal unpaired median neurons — VUM and DUM, respectively), which induce long-term effects both centrally and peripherally. It was thought that DUM neurons acted either as a kind of general arousal system — in fact, they seem to be either excited or inhibited depending upon the selection of motor programs. In the defence kick or jump, characterised by a sudden extension of the hindleg, the activation is begun by a coactivation of extensor and flexor muscles. However, the leg begins to move when the flexor muscles relax, while the extensors retain their activation. Throughout, the DUM cells are activated in parallel by specific motor neurons. Intracellular recordings from both types of cells demonstrate that they receive a common drive.

In some fictive behaviour, such as crawling in the larval butterfly *Manduca sexta*, all DUM neurons controlling thoracic and abdominal muscles are activated. In other behaviours, such as fictive flight in *Manduca*, there is a division of labor: DUM neurons controlling muscles involved in wing movements are inhibited, while DUM neurons directed to the leg muscles are activated. In fact, DUM neurons play an important role in the regulation of muscle metabolism, with octopamine controlling the glycolytic flux in muscles.

Kitai *et al.* (pp 690–697), like Pflüger, focus their review on the issue of neuromodulation. They discuss the firing patterns of dopaminergic (DA) cells in the pars compacta of the substantia nigra (SNc). This is an important issue, since we know that DA neuron firing represents a physiological mechanism which greatly influences activity in the rat forebrain. *In vivo*, in anaesthetized or awake behaving animals, DA neurons characteristically discharge multiple spike bursts. In contrast, DA neurons recorded in tissue slices *in vitro* display a stable, homogeneous tonic single spike activity. In the former case, but not in the latter, the SNc is under the control of both the subthalamic nucleus (STN) and the pedunculo-pontine nucleus (PPN). Afferent neurons from these two regions affect the SNc through both glutamatergic and cholinergic inputs.

The following hypothesis may explain the differences between the *in vivo* and *in vitro* findings. *In vitro*, inward and outward conductances contribute to the stable discharge of

the DA cells.  $\text{Ca}^{2+}$  entry resulting from  $\text{Na}^+$  spikes activates an apamin-sensitive slow potassium (SK) current, and causes an after-hyperpolarisation (AHP) that prevents bursts and thus maintains a tonic discharge. In comparison, *in vivo*, the patterned bursting activity is attributable to a combination of NMDA and ACh actions. Inputs from the STN and PPN result in inward currents, which depolarise the DA neurons. The bursting itself seems to be attributable to a reduction of the SK current. Modulatory cholinergic inputs from the PPN act like apamin; a reduction of  $\text{Ca}^{2+}$  entry may contribute to the reduction of SK current. Kitai *et al.* stress that DA neuron activity is not only attributable to the activation of NMDA receptors, but also to a combination of neurotransmitters and neuromodulators (such as ACh) that act in concert.

## Sensory-motor integration

### From network to cognition

The reviews by Sparks (pp 698–707) and Berthoz and Viaud-Delmon (pp 708–712) focus on the control of gaze and the displacement of the body in the environment. Both reviewers aim to relate the results obtained from investigations of the neural circuitries to cognition. Sparks focuses on activation of the superior colliculus (SC) in animals, and Berthoz and Viaud-Delmon on sensory integration during navigation in humans.

When stimulated, the SC produces coordinated movements of the eyes and head. Sparks asks the question of how these movements are represented at the level of individual collicular neurons. This review focuses on several fields of research that have recently highlighted the characteristics of the SC.

Sparks' review refers to the SC 'motor map', and he underlines the difficulties of integrating all the data obtained using different techniques into a clear picture of how such a map may arise. It seems that the collicular neurons encode different parameters of gaze, such as amplitude and direction. The complexities of the relations between SC activation, the vestibulo-ocular reflex (VOR) and saccadic movements are discussed in terms of central versus peripheral interactions. Sparks also considers the idea that several cognitive processes may influence the different parameters of saccadic eye movements and the discharge pattern of SC neurons.

Berthoz and Viaud-Delmon focus their review on the integration of neuronal activity with cognitive processes. They examine how spatial orientation during navigational tasks and locomotion depends upon the central integration of current multisensory information. These complex messages are integrated with planned trajectories, body schema and memories. Visual, vestibular and kinetic signals must be combined into a unique coherent percept, which seems to depend on internal models. The authors describe different methods used to study these complex interactions. Spatial orientation during navigation seems to depend on higher cognitive processes; Berthoz and Viaud-Delmon

focus on the relations of this motor behaviour with emotions. By considering agoraphobia and other pathological states, they speculate on the causes of the observed disturbances of sensory integration that are encountered by sufferers. They point out that dysfunction of the vestibular system leads to dizziness and disorientation. In 'space phobia', a false sense of orientation may arise from the inappropriate generation of sensory signals, and hence a resulting disordered central interpretation of sensory afferent coordination. Agoraphobic patients present abnormal instability when maintaining upright posture under sensory conflicting conditions.

The authors also analyse differences in space orientation between males and females. Different experimental data suggest some gender differences in the central processes dealing with visuo-vestibular interactions and internal strategies between spatial orientation and spatial memory. Why do these differences exist? Could the differences be due to the effects of sex hormones on the hippocampus? Further experiments are needed to clarify these interesting questions.

### Computational approaches

Both Mussa-Ivaldi (pp 713–717) and Kawato (pp 718–727) emphasize the idea that the acquisition of complex motor skills is facilitated by the formation of internal models, which are neural representations of the input–output characteristics of the motor system. These representations make it possible for the central nervous system to generate new behaviours and to react adaptively to new environments and new contingencies. Mathematically, the term 'internal model' refers to two transformations: first, the set of operations that change a motor command into motor behaviour (the so-called 'forward model'); and second, the set of operations needed to retrieve a motor command from motor behaviour (the 'inverse model'). Mussa-Ivaldi presents evidence indicating that the operation of internal models is based on elementary building blocks or 'primitives'. He identifies two types of primitives: one type is responsible for the control of limb dynamics, whereas the other type is needed for motor planning. The broadly tuned, non-linear force fields found in the spinal cord are thought to control limb dynamics. The populations of cortical cells that appear to represent motor goals (such as the cells described by Georgopoulos *et al.* [5] and Rizzolatti *et al.* [6]) play a role in motor planning.

Similar themes are discussed by Kawato. For instance, in his 'minimum variance model', he shows that both kinematic and dynamic internal models are needed for movement planning and for the control of limb dynamics. Kawato presents evidence supporting the existence of internal models, and points out that such models are probably located in all brain regions endowed with synaptic plasticity. Both neurophysiological investigations and imaging studies indicate that the cerebellum is the most likely site for an internal model of eye movements. When attempting to characterise the functional properties of internal models (a difficult but

important task), Kawato shows us that one approach is to ascertain their generalization capabilities. This is a topic of great interest, and Kawato does an excellent job of pointing out the relevant papers.

### Brain imaging and the understanding of motor functions

Both Rowe and Frackowiak (pp 728–734) and Jeannerod and Frak (pp 735–739) discuss how the development of non-invasive imaging technologies has led to new insights into the functioning of the motor system. Impressive technological advances have increased the spatial and temporal resolution of functional imaging; it is now possible to identify neurovascular responses in neighbouring cortical columns just 0.5 mm apart. Rowe and Frackowiak review a variety of fMRI studies: some of the investigations focus on the changes that occur throughout the motor system during voluntary movements, while other studies reveal the effectiveness of imaging techniques for the study of motor learning, the regional specialization within the motor system, and the mechanism of recovery after injury. Clinical and motor developmental disorders have also been investigated using imaging techniques. Rowe and Frackowiak convincingly communicate the potential of these novel techniques, the exciting and significant advances that have already been made, and those that are likely to be made in the future.

The studies reviewed by Jeannerod and Frak, like those of Rowe and Frackowiak, are based upon the utilization of various imaging techniques. Jeannerod and Frak's goals, however, are different: they focus on the use of 'motor imaging' as a tool for investigating motor functions. Motor imagery corresponds to 'subliminal' activation of the motor system. As pointed out by Jeannerod and Frak, there are two types of motor imagery: one is the conscious representation of an action; the other is an implicit motor imagery. The latter occurs when subjects 'automatically' make a judgement as to whether actions performed by others would be easy, difficult or impossible. Motor imagery has also been used to probe the degree of similarity between simulated and executed actions, as well as the extent of the involvement of motor areas during imagery. All in all, the studies reviewed by Jeannerod and Frak represent an important conceptual advance, and the area of motor imaging is likely to contribute significantly to our understanding of the cognitive aspects of the motor system.

### Recovery after damage to motor cortical areas

There is considerable recovery of motor functions after damage to the motor cortex, both in humans and other mammals. In his review, Nudo (pp 740–747) summarizes the neuroanatomical and physiological evidence demonstrating the circumstances under which recovery is likely to occur. The central point of the studies reviewed by Nudo is that the functional maps in the motor cortex are dynamically maintained by use of the corresponding body part. Following injury to the motor areas, repetitive use of the body part results in a change of motor representation in the spared cortex adjacent to the lesion. After motor skill practice in normal animals, the topography of representations in the motor cortex is altered such that newly learned movements are represented over larger cortical territories. There is also dendritic growth, and an increase in synaptic strength in the horizontal connections. Together with changes in excitatory and inhibitory transmitters, these alterations provide the substrate for the recovery of cortical functions.

### Closing thoughts

In conclusion, the reviews presented in this section of *Current Opinion in Neurobiology* attest to the intellectual vitality of the investigations conducted in the broad area of motor control. The exciting issues of motor planning, of controlling dynamic interactions with the environment and of motor learning have been investigated with a variety of approaches. In some areas, progress has been outstanding. For the future, the utilization of novel experimental techniques combined with the increasing sophistication of modelling tools bodes well for this area of research.

### References

1. Ben Ari Y, Khazipov R, Leinekugel X, Caillard O, Gaïarsa JL: **GABA<sub>A</sub> and AMPA receptors: a developmentally regulated 'ménage à trois'**. *Trends Neurosci* 1997, **20**:523-529.
2. O'Donovan MJ: **The origin of spontaneous activity in developing networks of the vertebrate nervous system**. *Curr Opin Neurobiol* 1999, **9**:94-104.
3. Crair MC: **Neuronal activity during development: permissive or instructive?** *Curr Opin Neurobiol* 1999, **9**:88-93.
4. McCormick DA: **Spontaneous activity: signal or noise?** *Science* 1999, **285**:541-543.
5. Georgopoulos AP, Kalaska JF, Caminiti R, Massey JT: **On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex**. *J Neurosci* 1982, **2**:1527-1537.
6. Rizzolatti G, Fadiga L, Gallese V, Fogassi L: **Premotor cortex and the recognition of motor actions**. *Cogn Brain Res* 1996, **3**:131-141.