The History of Neuroscience in Autobiography
Volume 9

Edited by Thomas D. Albright and Larry R. Squire
Published by Society for Neuroscience
ISBN: 978-0-916110-02-4

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pp. 108–135

https://www.doi.org/10.1523/hon.009004

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Docent in Physiology, Medical Faculty, University of Göteborg (1969–1975)
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Member of Academiae Europaea 1990–
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Member of Norwegian Academy of Science and Letters, 1997–
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Associate of the Neuroscience Institute, La Jolla, 1989–
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Florman Award, Royal Swedish Academy of Science, 1977
Grass Lecturer to the Society of Neuroscience, Boston, 1983
Greater Nordic Prize of Eric Fernstrom, Lund, Sweden, 1990
Bristol-Myers Squibb Award for Distinguished Achievements in Neuroscience, 1993
Reeve/Irvine Research Medal, New York, 2002
Neuronal Plasticity Prize, Fondation Ipsen, Paris, 2003
Ralph Gerard Prize, Society for Neuroscience, Washington, DC, 2005
Ragnar Granit Prize, Finland, 2006
Linnéan Zoology Award, Lund, Sweden, 2007
The Kavli Prize in Neuroscience, United States/Norway, 2008
The King's Medal–Band of the Serafimer Order, Sweden, 2012

Sten Grillner is a neurophysiologist with a focus on the cellular bases of motor behavior, initially in mammals, but later utilizing a lower vertebrate model, the lamprey. This has enabled him to unravel intrinsic functions of microcircuits generating locomotor movements at the brainstem–spinal cord level, the midbrain control mechanisms for steering, and the forebrain mechanisms underlying selection of behavior. His research extends from ion channels and synapses to network mechanisms utilizing a multitude of techniques. On the basis of detailed experimentation, he has successfully modeled the networks underlying locomotion including steering and posture. The lamprey central nervous system is evolutionary conserved and serves as a blueprint of the mammalian motor system.

Sten Grillner

My first memories are from Filipstad, a small picturesque town in western Sweden with a long tradition of mining, where my father was physician and responsible for the health care. We later moved to Norrköping, a midsize city, south of Stockholm, where I went to school to finish in 1960. I have fond memories from this time and had rather broad interests, perhaps more toward literature than science. My parents were always supportive, and they let me follow my own inclination. My exposure to research was limited, although I had an uncle geologist, who explained his different projects with great enthusiasm, which I found interesting.

I was uncertain of what I liked to study but finally decided on the Medical Faculty in Göteborg (Gothenburg), and was moderately engaged in the curriculum, until the course in physiology, which I found quite interesting, in particular, neurophysiology. After the course, I was allowed to join Anders Lundberg's laboratory as an unpaid amanuensis, in parallel with the continued studies. This was a stimulating environment with visiting scientists from all parts of the world. During the first summer, I was allowed to explore a project I had come up with myself. Do the cells of the adrenal medulla (of neural origin) display action potentials when activated? I failed—although I could occasionally impale these cells, I was not able to hold them because of arterial pulsations. Later it was shown that they indeed could generate action potentials.

The First Steps toward Becoming a Neurophysiologist

I subsequently learned neurophysiological techniques together with Staffan Lund, an older graduate student, and Toshinori Hongo, a postdoc from the University of Tokyo who later became head of the Brain Research Institute at this university. I very much enjoyed working with both of these colleagues, and together we carried out a series of studies on the fast conducting vestibulo- and reticulospinal pathways, which we found to have direct monosynaptic connections to extensor and flexor motoneurons, respectively. These studies, still cited, were cutting edge at the time. One day, a fellow student asked me, what is their role in the behaving animal: I then realized that we simply did not know, we could just infer their role. This made me understand the need to relate the cellular findings to behavior, if they were to provide insight related to brain function.

My thesis dealt with the supraspinal and segmental control of gamma-motoneurons that control the sensitivity of muscle spindles. It also addressed

how these neurons became activated during the late reflex discharges induced after injecting the noradrenergic precursor dihydroxyphenylalanine (DOPA) in the spinal animal. Lundberg and colleagues had proposed that these discharges result from an activation of part of the locomotor network. I could show that, indeed, the gamma-motoneurons become activated in parallel with the alpha-motoneurons.

In Lundberg's laboratory, the PhD students were rather independent and left to their own initiatives, but in a stimulating environment. He was involved mainly in reviewing the manuscripts—but he did not co-author them unless he had been running the experiments himself—a practice that is quite different today but common at the time. This fostered independence but could be difficult for some students.

This gave me freedom to explore alternative routes, and I found that DOPA also induced tonic stretch reflexes, a finding that many colleagues found interesting, including Ragnar Granit, the Nobel laureate of 1967, who was encouraging and supporting. This finding was closer to behavior, and therefore I found it particularly interesting. After completing my PhD, I further analyzed the recruitment pattern of motor units, and the role of muscle properties for load compensation during standing and locomotion. These studies led me to emphasize the importance of muscle properties (length–tension curves), and I found myself opposing Peter Matthews, the spindle authority at the time, in his argument for a sensory contribution of the group II spindle afferents. This led to a public and rather intense discussion.

Another result that I found interesting during my thesis work was that after administration of DOPA, several bouts of alternating flexor and extensor activity could be elicited in the spinal animal. In addition, and as important, I could induce alternating limb movements resembling locomotion in a spinal animal with no further operation. This experiment, which was reported on in only a few lines in my thesis, had a major impact on my future research. I found these results satisfactory, and from then on, I was hooked on motor control and the neural bases of locomotion. In May 1969, I defended my PhD thesis within the Medical Faculty.

Postdoc in Moscow in the Middle of the Cold War

Instead of going to Harvard for a postdoc in the Physiology Department to study the properties of stretch reflexes, as originally planned, I decided to spend 5 months at the Academy of Science in Moscow, in the middle of the Cold War. The reason was that Grigori Orlovsky and Mark Shik had developed a reduced preparation (without forebrain) that allowed detailed studies of the neural control of locomotion and posture. They had shown that stimulation of a circumscribed area in the midbrain (the mesencephalic locomotor region, MLR) could elicit well-coordinated locomotor movements

on the treadmill. This opened up the possibility to study the neural bases of motor behavior, without the ethical constraints that limits experiments on intact animals or the need to use animals under anesthesia.

We then could show that subthreshold activation of MLR indeed released reflex discharges similar to that of DOPA and a suppression of other short-latency responses. We then suggested that the MLR indeed caused locomotion by releasing the spinal network activated by DOPA. This is still a valid conclusion, but now not only the noradrenergic but also the glutamate and 5-hydroxytryptamine (5-HT) systems are known to contribute. In the Moscow Laboratory, the research groups tended to have interesting questions, but at the same time outdated equipment. I was even recording rapid events with a mirror galvanometer—a piece of equipment used before oscilloscopes emerged—but it was to the point for our questions.

I interacted closely with Orlovsky, who performed elegant and technically demanding experiments on the fast-descending tracts modulated by cerebellum during each step cycle, and the pathways to cerebellum that conveyed information on the ongoing movements, as well as efference copy information about the spinal commands. Novel findings. Typically, Orlovsky was running the actual experiments with his special skills, but around him stood several colleagues, often smoking, with different expertise (physics, mathematics, biology) discussing the possible significance of the findings. He thus had a group with different background training but with a focus on understanding the same mechanisms—an excellent strategy for success in science.

The laboratory at the Academy in Moscow was high profile, led by Israel M. Gelfand, a renowned mathematician who later received the Kyoto Prize. For example, in the evaluation of different reports in seminars or workshops, the focus was explicitly on whether or not new fundamental insights had been gained. If an elegant study made with the most refined novel techniques reported just a new fact, without at the same time leading to new understanding, Gelfand and colleagues were not impressed. This was an important take-home message. Still today, the area of neuroscience is characterized by an accumulation of facts and much less of synthesis.

The Social Life as a Postdoc at the Academy

To Moscow, I came alone traveling in midwinter through Finland, Leningrad, and Novgorod in a big Volga I had bought in Sweden—an adventure in itself. As I arrived in Moscow, I was installed in the Hotel of the Academy of Science together with scientists from all around the Soviet Union, in itself an interesting experience. For breakfast I usually had tea and bread, while my senior Russian colleagues in the cafeteria, often with a sign of political distinction, not rarely would have a full drinking glass of Russian cognac.

The time in Moscow in the middle of the Cold War was a great experience personally as well as scientifically. During the first few weeks, my many colleagues seemed friendly but somewhat reserved, but once they accepted me as a reliable human being (particularly important in a society in which informers could be expected at any instant), the conditions changed. The laboratory was composed of a nice set of colleagues, many of Jewish origin that took extremely good care of us all at a personal level. My wife Lena (a medical doctor) joined me after some weeks (with a separate grant in parasitology), together with our two daughters, ages one and three, and a very nice au pair, Lena Larsson, from Göteborg.

We had a lovely time not only for science but also for interactions with my colleagues, in particular Orlovsky and his family in addition to Mark Shik, Olga Fucson, Sergeij Kashin, and Yuri Arschavsky. They made us understand the many interesting aspects of Russian culture, older and contemporary art (the latter shown unofficially), literature, history, and so forth. At the same time, they made us realize how difficult it was to live in a society where everybody assumed that the telephones were bugged (including in our flat), where one does not quite know who could be informers to the KGB (the main security agency) or the local scientific Soviet. This was a scary society in which to live. The children of dissidents had difficulties gaining admission to universities, not to speak of the difficulties encountered by the dissidents themselves. And yet the situation had improved markedly from the times of Stalin, when one could be sentenced for even speaking to a foreigner.

Back in Göteborg—Spinal Organization of Locomotion in Mammals

When I returned home to Göteborg, as a young PI (principal investigator), I had the fortune of getting competent postdocs and visiting scientists like Serge Rossignol, Reggie Edgerton, Claude Perret, and Sergei Kashin, as well as graduate students like Peter Zangger, Hans Forssberg, and Peter Wallén. We had a productive period establishing that the spinal cord networks in cats could generate the detailed motor pattern underlying locomotion, but that these networks indeed were assisted by a number of well-designed sensory reflexes that adapt the motor pattern to outside events.

Spinal Animals Can Generate Locomotor Movements

One important finding was that animals (cats) that had received a transection of the spinal cord (thoracic level) in the first few weeks after birth could generate well-coordinated locomotor movements, as would adult animals, when the spinal cord was activated by DOPA or noradrenergic agonists. When the hind limbs of the spinal animals were put on a moving treadmill

belt, with the belt speed set on low, the two limbs generated alternating locomotor movements. But when the speed was increased, the coordination of the limbs changed to in phase locomotor movements like in a gallop. This thus demonstrated that the two basic modes of coordination could be generated by the spinal cord devoid of any influences from the brain. When the detailed motor pattern was recorded, in terms of electromyography (EMG) of the different limb muscles, the pattern was virtually identical to that of the intact animal. We thus concluded that the spinal cord networks with sensory input indeed could generate the detailed locomotor programs, rather than just simple alternating movements. Although reports from Charles Sherrington and others had indicated that alternating muscle activity could be produced in spinal animals, it was a different thing to show that the actual movements and EMG pattern could be generated in a spinal animal.

Rossignol in Montreal has over the years continued this line of research in an elegant way, showing that these conclusions also apply to mouse and rat—for a long time claimed by some not to follow this scheme. This has been a problem in many reports of spinal cord injury research, claiming functional regeneration over the lesion, when in reality the spinal central pattern generator networks (CPGs) have been recruited into action. Edgerton, who spent some time in the laboratory in 1975, also has worked along these lines over many years. Inspired by our old spinal cat experiments, and his own, he initiated a training programs for patients with spinal cord injury similar to that used to train the spinal cats. This human work is forcefully continued by Susan Harkema, Edgerton's previous collaborator, and has been successful for patients with partial spinal cord injury.

Central Pattern Generator Networks Provide Detailed Timing

The next-level question was to ask how much of this control depends on networks within the spinal cord, and how much is dependent on sensory input from the moving limb. We could show that the intricate motor pattern with timing of the different muscles in the step cycle could be retained after all afferents to the limb had been transected by cutting the dorsal roots and thereby abolishing the sensory input from the moving limb. This clearly established that the networks in the spinal cord itself could coordinate the timing of the different muscles active in the step cycle.

These findings also showed that the favored hypothesis at the time was incorrect. It assumed that the spinal central networks would generate a simple flexion extension pattern (as Graham Brown indicated), on which afferents were to sculpt the final pattern and produce the characteristic complex motor pattern observed during locomotion (with the reflexes identified by among others Lundberg). We showed, in contrast, that the spinal cord networks themselves could generate the timing. For many years, the proponents of the original hypothesis had difficulties accepting that it

was simply incorrect. This led to undue tension with my former supervisor Lundberg and unfortunate animosity lasting throughout his life, which has been perhaps the most depressing experience of my scientific life. Something that I had not imagined would ever happen, when I set out to do these experiments. I believe, as a researcher, one should strive to explain the existing findings in the most rational way—nothing is wrong with an incorrect hypothesis, as long as the experimental findings are correct. We thus demonstrated that a characteristic of the locomotor system was the presence of networks (CPGs) within the spinal cord that contained the necessary information to generate the coordinated activation of the different muscle groups.

Sensory Input Interacts with the CPG

The presence of CPGs in the spinal cord does not mean that sensory information arising during the movement is not of major importance. The ability of the sensory input from the moving limb to adapt the movements to the actual mechanical events is critical. Rossignol and I defined one main factor adapting the step cycle in relation to the position of the hip in each step. We could show that, when the limb had reached a posterior position, the sensory input from the hip helped trigger the transition to flexion—a critical mechanism in the control of locomotion. In parallel, Keir Pearson and colleagues showed that receptors signaling the load on the limb also were providing important feedback.

Throughout most of the 20th century, it appeared to be a sometimes-bitter rivalry between two camps: those that argued for a dominance of central networks such as Brown and Erich von Holst and those that were focused on the sensory contribution like Sherrington, James Gray, and H.W. Lissmann. In 1985, in an article I published in *Science*, I emphasized the need to consider both aspects to have a successful locomotor control, and I thought I had put this rivalry to rest, but some years later one-sided arguments for one side or the other still popped up and continue to do so. Despite a clear demonstration that both aspects are critical, this type of difference persists to some degree—most researchers tend to overemphasize the importance of what they currently are doing. The tendency to do so has increased with the unfortunate emphasis in later years on impact factors in scientific publishing.

Phase-Dependent Reflex Reversals and Placing Reactions

Another unexpected mechanism was our demonstration of a phase-dependent reflex reversal. A sensory stimulus to the dorsum of the paw would generate an enhanced flexion, if it occurred during the swing phase of the step, but the identical sensory stimulus instead would lead to an

enhanced extension, if it occurred during the support phase. This central gating of the reflex response is behaviorally meaningful in that a limb touching something during the swing phase should try to instantaneously overcome the obstacle by an enhanced flexion. Conversely, if the same stimulus occurred during the support phase, it could be disastrous, if it led to a flexion that would make the limb collapse; therefore, it is functional to instead have an enhanced extensor activity. This provides an example of a clever design that the spinal cord has developed during evolution.

In Search of an Experimentally Amenable Model to Study the Intrinsic Function of the Locomotor Networks: First Dogfish and Then Lamprey

My central interest at the time was to understand not only that spinal networks were coordinating locomotion but also their intrinsic mode of operation. We started to explore the neuronal activity that took place when the mammalian network was active, but we soon realized that recordings of interneuronal spike activity did not provide sufficiently rigorous information to understand how a network operates. Much more precise information was needed, and I started to search for a simpler experimental model that still needed to be a vertebrate, if the knowledge obtained ultimately would be regarded as a model system for mammals.

The first candidate was the dogfish (a small shark). It had a special methodological attraction in that the spinal cord continued to generate swimming movements even after a transection of the spinal cord, as demonstrated by A. Bethe and I. Steiner at the end of the 19th century. Pharmacological or electrical activation thus was not needed. In August 1972, I set up a laboratory at the Marine Biology Laboratory of the Academy of Science, at Kristineberg, a scenic site on the Swedish west coast for a few months. This was a lovely environment, and it was excellent that they required no fees and collected the dogfish without any costs for me (quite different nowadays). For me, it was also a new and an interesting environment—a mix of a variety of researchers from ecology to biophysics with interesting goals in mind. For a decade, Wallén and I had a lab for a few months each year at Kristineberg.

At the time, it was thought that the locomotor movements in the dogfish resulted from a chain reflex, as argued by Gray and Lissmann in Cambridge, England. Zangger and I could show, on the contrary, that after inactivation of the sensory input, the spinal cord could generate rhythmic activity recorded in the ventral roots. Moreover, the phase-lag between rostral and more caudal segments that generate the propulsion during swimming remained after deafferentation. Thus, as in mammals, the shark spinal cord contains a CPG network that generates the basic locomotor coordination.

What about the sensory contribution? Wallén as a young PhD student could show that the sensory input that occurs during the locomotor movements can entrain the CPG network at frequencies above or below the basic frequency of the CPG network at rest. Thus, the sensory input could drive the spinal CPGs, a finding that we later could show applied also to both mammals and lamprey. In other words, a central spinal generation of locomotion was combined with a sensory modulation of the movements.

It turned out, however, that the dogfish spinal cord was technically less favorable when it came to intracellular recordings from several neurons at the same time. On the one hand, for the first time, we had demonstrated that in fish (as in cats) an organization with a CPG was assisted by sensory input from the moving body. On the other hand, we could not pursue our ambition to get at the intrinsic mechanisms of how the spinal network operates.

After experimenting with the dogfish for a few years, we instead zoomed in on the lamprey, which represents the first group of vertebrates to evolve, but with all parts of the vertebrate nervous system already present. Because of its strategic position in vertebrate evolution, a reasonable amount of neuroanatomy was available, starting with two papers of the young Sigmund Freud, then still a neurologist, and many others to follow in the early middle part of the 20th century. Another important factor was that some basic cellular neurophysiology was available from Carl Rovainen's studies starting in 1967.

Moving to Stockholm

In 1975, the Swedish Government appointed me to a professor position, at the Department of Physiology III of the Karolinska Institute. In January 1976, I moved my laboratory to Stockholm. Two of my graduate students Forssberg and Wallén joined me, and together the three of us rapidly managed to build up the new laboratory. Forssberg continued the experiments on the phase-dependent reflex reversal in cat, while Wallén was engaged in developing the lamprey spinal cord as a viable preparation, together with Avis Cohen, who joined as a postdoc. We presented our first lamprey report in Paris at the International Union of Physiological Sciences meeting in 1977.

At the time, I also had received funding for setting up a computer-based movement laboratory for recording EMG, forces, and movement together. At this time, this was a demanding task, as the computers were far from what they are today. Another student with a physics background from the Netherlands, Junt Halbertsma, helped develop the laboratory, which was to become, for some time, one of the best equipped movement laboratories anywhere. Forssberg and Halbertsma did nice studies on the cat, correlating movement and behavior. Forssberg further initiated studies on the development of walking in children from the early stages and onwards, which

he continued in the pediatrics department. He later became professor at Karolinska's children's hospital and provost of the Karolinska Institute.

I also initiated an independent group led by Alf Thorstensson (PhD) that used our new movement, force, EMG recording system to study human locomotion and equilibrium control with a focus on the trunk and adaptations to speed and load. This provided a series of important studies on basic aspects of human locomotion that required the new digital technology developed to measure motion through multiple light-emitting diodes (referred to as the Selspot system) just being available at the time, and the adaptations of the motor pattern that occur as the speed increases and if a load is carried. These data have served as controls for considering clinical movement deficits. Thorstensson continued the development of this laboratory and later became professor in biomechanics.

The Lamprey Model—The Intrinsic Function of the Spinal CPG

The development of the lamprey as a model system for understanding the intrinsic function of the CPG was without question the main aim of my research at this time. We had to investigate this in systematic fashion step by step, showing first that the isolated spinal cord could generate coordinated locomotor activity when excited by stimulation of the spinal cord, or better, by bath-applying glutamate or its agonists. Glycinergic crossed inhibition was found to generate the alternation between the left and right side. On the other hand, we could show that the hemicord (separated along the midline) could generate rhythmic burst activity without glycinergic inhibition, which was an important piece of the jigsaw puzzle provided by Lorenzo Cangiano. Wallén and later Lennart Brodin used pharmacology to analyze the network and demonstrated the role of glycinergic transmission as well as glutamatergic transmission, and also revealed how NMDA and AMPA receptors contribute in separate ways to the network operation. The oscillatory properties induced by NMDA were another important feature that we explored (with Karen Sigvardt and Wallén). The identification of cellular properties, subtypes of ion channels, and the identification of calcium-dependent potassium channels were important steps toward understanding network operation.

After these baseline studies, we had ideal conditions to start to probe for interneurons with paired recordings between pre- and postsynaptic neurons. Wallén and I detailed the motoneurons together with Jack Feldman, on sabbatical from Northwestern, and showed that they received periods of excitation alternating with inhibition and had an intricate morphology—the latter being a critical piece of information. On the ipsilateral side, excitatory premotor interneurons were identified, initially through stimulation of single axons by Nick Dale. The final important demonstration of glutamatergic premotor interneurons of the network and their connectivity was

achieved through paired recordings between the presynaptic interneurons and the postsynaptic neurons. Jim Buchanan and I published these findings in *Science* in 1987. These data were critical for understanding the network design and provided the bases for the initial network simulations.

Some years later, Simon Alford and Abdel El Manira joined the laboratory, and we then uncovered a phasic presynaptic modulation that occurs in each swim cycle. It occurs not only in sensory afferents, but also in both inhibitory and excitatory premotor interneurons. This means that the synaptic efficacy will vary throughout the swim cycle, which was an important finding. As yet, the presynaptic modulation of premotor interneurons has been demonstrated only in lamprey, but the difficulty of these experiments is so great that no serious attempt, that I am aware of, has been made in other species. Most likely it also occurs in mammals. Alford has continued elegant studies on synaptic transmission in his own laboratory in Chicago. El Manira, now for many years professor at the Karolinska Institute, has uncovered many intriguing aspects of metabotropic control at the synaptic, cellular, and network level in lamprey, in recent years working mostly in zebrafish.

The metabotropic modulation of neuronal properties (ion channel subtypes) on the presynaptic and cellular level represents a central control of network function exerted via aminergic, peptidergic, and metabotropic GABA and glutamate receptors (mGluRs). These different modulator systems are of critical importance for the fine-tuning of the network operation and has been the focus in a long series of studies, including not only by El Manira but also by Wallén, Russell Hill, Martin Wikström, Toshiya Matsushima, Fulvia Bongianni, Weiqi Zhang, Judith Schotland, and Di Wang.

Modeling—An Indispensable Tool for Network Analyses

After several years, in 1987, the main players in the network had been identified. We could characterize the network underlying locomotion and the connectivity of both excitatory and inhibitory neurons, their transmitters, and their membrane properties. We then had sufficient information to test whether the detailed knowledge we had acquired could account for the behavior—and the only way to achieve this was to use modeling in which the model neurons "expressed" the same type of ion channels as did their biological counterparts, that is, each model neuron was a close replica of its biological cousin. The model neurons (network interneuron subtypes) interacted synaptically, as found experimentally through subtypes of glutamate (NMDA and AMPA) and glycine receptors. We then were able to show with Anders Lansner at the Royal Institute of Technology (KTH) in Stockholm that the components we had identified, indeed, could account for the locomotor behavior. The model network, constrained by detailed experimental

data, could reproduce all aspects of its biological counterparts with regard to network performance. This meant that the experimental evidence obtained could account for the behavior.

Jeanette Hellgren, then a graduate student, extended these simulations from the single segment level to intersegmental coordination, incorporating phase coupling to produce the undulatory wave that moves the lamprey forward. This advance was based on a series of physiological experiments that involved Matsushima. This collaboration still continues, and it has been immensely useful to make *in silico* experiments and interact both ways between biology and simulation—to study, for example, the contributions of different subtypes of ion channels to network function.

Recently, with Hellgren and Alexander Kozlov, we simulated the entire brainstem–spinal cord network that generates the locomotor activity. The appropriate number of neurons was simulated with great precision using a Blue Gene supercomputer. This simulation includes network locomotor activity, steering, and initiation of locomotor activity from the basal ganglia (see the following). Moreover, we also have included neuromuscular simulations, in which the network controls a model lamprey swimming through simulated water.

One interesting finding that came out of these large simulations was that the variability of cellular properties that had been observed experimentally was actually important. If all neurons of a given class were given the same properties (e.g., average of input resistance, ion channel composition), the network was less stable and operated only in a limited range. If, however, the observed variability was introduced, the network performed much better because the model neurons were recruited in a gradual fashion. Essentially, we could conclude that the variability observed experimentally was an evolutionary design feature and not a mistake by nature.

Our knowledge of this network is now so detailed that we can predict what effect a modification of a gene-product like an ion channel in a given type of neuron will have on the activity of these neurons, and how it will affect the network and ultimately the locomotor behavior. We thus can go from a modification of a gene product (e.g., ion channel availability) over cell, synapse, and network to behavior. Many of the modulator systems that we have characterized (e.g., GABA-B, mGluRs, 5-HT, dopamine, peptides) act on different ion channels. Simulating the action of different modulators on the single cell level in the model network has often explained the overall network effects observed experimentally. In this system, we can bridge from gene to behavior, which is a rare occasion in other systems.

How the Simulation Team Evolved

When we started the simulations in 1987, Wallén, Brodin, and I provided the biological basis for the project, while Lansner, Örjan Ekeberg, and Hans

Tråvén were the computer scientists, interested in simulating the nervous system. It was important to align our competences, so we spent a lot of time in the beginning getting through the biophysics of the nervous system, like the Hodgkin–Huxley equations, and the systems biology, while we also went over the different ways of making efficient and fast simulations. This was an important process in that we then acquired a common language to interact in a creative and productive way. We were able to bridge the gap between biology and physics–computer science to a large degree. We obtained a common grant for simulation from the Science Research Council in 1987, which still funds this collaborative research program. Through this collaboration, we have produced a long series of studies, which have been critical for the understanding of the microcircuits and networks of the lamprey. A series of PhD students, with a combined background in neuroscience and modeling, graduated. Lansner had completed his PhD before we started this collaboration, but Ekeberg, Tråvén, Tom Wadden, Jesper Tegnér, and Hellgren participated as PhD students and postdocs partially financed through this grant. Some decades later, they are professors at the Karolinska Institute (Tegnér) and at the KTH in Stockholm (Hellgren and Ekeberg); Tråvén took a position in industry and Wadden returned to Canada.

Immunohistochemistry—Interaction with Tomas Hökfelt

Although my laboratory has been oriented primarily toward neurophysiology, it became apparent that structure was an important aspect to understand function. The first step was the utilization of intracellular dyes, like Lucifer yellow or horseradish peroxidase, to elucidate the dendritic morphology of motoneurons and interneurons in the spinal cord and to determine their detailed morphology (important for the simulations) and axonal projections, and possible synaptic contacts.

In the 1980s, we started to use immunohistochemistry to identify putative transmitters and peptides in the different cell types in the brainstem and spinal cord. We completed an extensive mapping of the brainstem–spinal cord mostly in collaboration with Tomas Hökfelt, who provided outstanding expertise. We collaborated over many years in an enjoyable and positive atmosphere while describing the morphology of the lamprey central nervous system utilizing optimal methods. Through Hökfelt, we had the expertise required not to make mistakes. A series of collaborators were engaged like Paul van Dongen and Brodin, with whom we described the 5-HT, dopamine, and a number of peptidergic systems, often in combination with retrograde transport of different markers to identify the axonal projections to different areas. Oleg Shupliakov extended our repertoire to electronmicroscopy (EM)—and in particular immunoEM—to be able to identify glutamatergic, glycinergic, and GABAergic transmitter vesicles. This was important for identifying transmitters at the synaptic vesicle level and other different

aspects. Brodin and Shupliakov are now, and have long since been, professors in the Department of Neuroscience at the Karolinska Institute.

In the past decade, Brita Robertson, an outstanding and likeable colleague, joined the laboratory, and we used the same methods to explore the intrinsic circuitry of the forebrain with the basal ganglia, habenulae, dopamine system, and cortex (pallium) with astounding results. Robertson continues to supervise several excellent postdocs or students using these techniques, including Marcus Stephenson-Jones, Elham Jalalvand, Kazuya Saitoh, Juan Perez-Fernandez, and Lorenza Capantini.

Development of 3D Confocal Microscopy—Interaction with Nils Åslund

In the early 1980s, we started to interact with Nils Åslund and his team in the physics department of KTH. They had started to develop three-dimensional (3D) confocal analyses—but only two dimensional was becoming available at the time. We realized the great advantage of having accurate reconstruction without the laborious procedure of redrawing the shape. Their 3D confocal microscope was first tested on our Lucifer yellow–stained cells from the lamprey. In particular Wallén from our side was deeply involved over many years. After some time, they developed a microscope called Sarastro, after a figure in Mozart's opera *The Magic Flute*, and started a small company to sell what was, at the time, the only confocal microscope to accurately create 3D images with good control of the z-axis. The first microscope was placed in our laboratory with the promise to provide demonstrations when needed. For a period, the Sarastro confocal microscope was the best on the market. After some time, the big players in terms of economy took over the market like BioRad, Zeiss, Leica, and Nikon and Åslund's company was bought up. With better economic backing for Åslund's group, the situation could have been quite different.

Moving up to the Brainstem and Forebrain Level

Brainstem Control—Locomotion, Body Orientation, and Posture

We showed very early, with Andrew McClellan, that lamprey locomotor activity could be initiated from the brainstem level corresponding to the MLR and an activation of reticulospinal cells. Rejean Dubuc has studied MLR in much greater detail, later in his own laboratory in Montreal. The ascending control from the spinal cord to the brainstem level was the focus of studies carried out by Dubuc and Laurent Vinay, which led to the demonstration that that the spinal CPGs forwarded information to the brainstem level to elicit a phasic modulation of cells in the different reticulospinal nuclei. The functional significance of this modulation was elaborated in a recent modeling study with Kozlov and Hellgren.

Another critical aspect in the control of motion is the ability of most animals to stabilize their body orientation during locomotion, whether flying, walking, or swimming. In 1989, when Russia opened up, during *Glasnost*, it was possible for my colleagues Orlovsky and his wife and colleague Tatiana Deliagina to come to Stockholm as visiting scientists. Rather than returning, they have remained in Sweden and are now Swedish citizens. They have become an essential part of our common laboratory and have contributed importantly to the lamprey work but also have continued their independent work on mammals.

Orlovsky and Deliagina have focused on the control system stabilizing body orientation, through elegant experiments in which the vestibular control of the brainstem circuits has been analyzed in the isolated brainstem with the vestibular apparatus being intact. This work has allowed for an identification of the circuitry and connectivity in this control system and for the demonstration of separate inputs from the vestibular apparatus to different classes of reticulospinal neurons, each responding maximally at a different body orientation. The total impact of the impressive work conducted by Orlovsky and Deliagina, sometimes working collaboratively with me, has led to an understanding of this complex control system. The lamprey, as an aquatic creature, relies primarily on the vestibular apparatus for this control. There is also an interaction with visual input, but the vestibular signals dominate. In terrestrial animals, there is an additional input from the limbs, which Orlovsky and Deliagina have detailed in a series of studies on mammals. These lamprey experiments are technically demanding, and they have been possible only through the outstanding experimental skills of Orlovsky. This represents a critical part of the control system for motion: without the control of body orientation, no meaningful control of behavior would occur.

Optic Tectum Eye—Orienting and Evading

To understand the control of motion, particularly in relation to steering, we explored the lamprey optic tectum, which corresponds to the superior colliculus of mammals. Kazuya Saitoh and I therefore started to investigate the effect of stimulating different parts of the optic tectum and found that we could elicit eye movements in different directions in a site-specific way. We also could elicit orienting movements of the head and trunk and evasive movements that would be used to avoid an obstacle. Thus, there was a motor map in the optic tectum, as in other vertebrates. We subsequently investigated the input from retina and showed that there is indeed a retinotopic projection pattern, and a sensory map matching the motor map. The microstructure of the optic tectum is similar to that of other vertebrates, and the output neurons are of two types: those that project to the ipsilateral reticulospinal neurons, and a smaller subpopulation that have

crossed axons and activate contralateral reticulospinal neurons. This is the neural substrate for either eliciting orienting movements toward an object (contralateral axons) or evasive movements to avoid an obstacle or predator (ipsilateral axons). Along with Andreas Kardamakis, we then explored the control of the output neurons from the eye and established an intricate organization in which an input from retina would activate a selected group of tectal output neurons, whereas all other parts of retina would provide a prominent inhibition. This was also the substrate for considering the possibility of a selection between two different visual objects, which would compete for attention. The most prominent would win—a winner-take-all arrangement.

We took up this area of research because we needed to explore steering in the context of locomotion. We also needed to consider selection of behavior not only in terms of locomotion but also in terms of steering the movements toward left or right and up or down. In this process, one needs to have input to the locomotor centers as well as to the tectal motor map for steering movements. In this context, the basal ganglia play a major role, as does the region of pallium/cortex that has motor projections to tectum.

Selection of Behavior—The Lamprey Blueprint of the Mammalian Forebrain

Having elucidated the basic organization underlying locomotion, control of body orientation, and steering, the next step was to understand the mechanisms that determine when a given motor program should be called into action. This required an understanding of the forebrain structures. In mammals, these different capacities can be generated in an automatic fashion in decerebrate animals (those lacking forebrain). The goal-directed aspect of behavior, however, requires that the forebrain remains intact to reach defined goals. In particular, the basal ganglia appears critical for this goal-directed aspect as well as the dopamine reward system, the habenulae, and the frontal lobe.

My expectation was that we would find a simplified organization for the control of the limited behavioral repertoire of the lamprey. I had begun work on this topic with Manuel Pombal and El Manira in the late 1990s. A major effort, however, started later with Stephenson-Jones, Robertson, and Jesper Ericsson. We set out to explore the organization of the basal ganglia and related structures. To our surprise, we found that the detailed organization of the basal ganglia in mammals was also present in the lamprey. This finding applied to the detailed organization of striatum, with the two types of projection neurons corresponding to the so-called direct and indirect pathways. The input from pallium/cortex, with two types of projections, also was present as well as a prominent thalamic input. Additionally, the ion channel expression was similar, and also the transmitters and peptides of

the projection neurons and of the interneurons. Moreover, the two output nuclei (globus pallidus interna and substantia nigra reticulata) and the subthalamic nucleus also were found to have similar characteristics to those of the rodent basal ganglia.

The detailed similarities we established meant that the structures must have been present at the point in vertebrate evolution, when the line leading up to the lamprey separated from that to mammals. This happened around 560 million years ago. It follows that the basic organization of the basal ganglia and related structures was present early in vertebrate evolution and has remained virtually unchanged. We have inferred that the basal ganglia are subdivided into modules that can release a given motor program. These modules contain the circuits to initiate a motor program and also to suppress competing motor activities. The lamprey would have rather few modules corresponding to its restricted behavioral repertoire. During evolution, a progressively increasing number of modules have been added, corresponding to an increasingly sophisticated behavioral repertoire from lamprey to primates. In evolutionary terms, this process is called *exaptation*. An analogy is the progressive increase in the number of cortical columns from mice to men.

The Motor Projections from Pallium/Cortex Are Evolutionary Conserved

Recently, we also set out to investigate whether pallium (cortex in mammals) could have a motor function, and if so, in what respect. We could show, contrary to expectations, that stimulation over a restricted area of pallium could elicit eye and orienting movements as well as oral movements and locomotion. Thus, there seems to be a type of motor cortex. We then could show that from this area, there were separate projections to the optic tectum (superior colliculus), reticulospinal neurons, and the spinal cord, as well as other target areas corresponding to the mammalian projection pattern. Essentially, we had established that the identical pattern was present in lamprey, as previously found in mammals. The lamprey system is thus a sort of blueprint of the mammalian system also with regard to pallium/cortex. At the same time, one must realize that, for instance, the projections to the spinal cord in lamprey can serve only to generate movements of the head and trunk, because limbs are yet to evolve.

Karolinska Institute and Neuroscience

I initially was working in Physiology Department III and was recruited to the Nobel Institute for Neurophysiology in 1986. This was an ideal time with comparatively good resources with staff and infrastructure from the university. I had over the years the good fortune of having a stimulating environment with several groups with converging interests. In my own

group, I was fortunate that Wallén decided to remain as senior lecturer in my laboratory; Hill (docent) was responsible for the technical development over many years; and, in 2005, Robertson joined, providing other expertise. In the early 1990s, the Orlovsky–Deliagina group would get positions initially through the research council; El Manira moved up the ranks to full professor and formed his own laboratory focusing on zebrafish; Ole Kiehn came from Copenhagen in the beginning of 2002 with his focus on the locomotor CPG in mouse, combining genetics with neurophysiology; and Gilad Silberberg, initially a postdoc in our group, is now an associate professor working on the rodent basal ganglia. Finally, Hellgren, while professor in neuroinformatics at KTH, has supervised PhD students and occupies an office in our department, bringing her modeling expertise to bear on these research problems. This has become a positive and interactive environment with common seminars and social interaction between PhD students, postdocs, and the many colleagues. Over the years, I have had more than 50 postdocs, many from North America, and some 16 PhD students.

In the late 1980s and early 1990s, I was quite active in the faculty board and engaged in restructuring the faculty from having some 140 mostly small departments to around 25 large departments in 1993. In this process, we created a neuroscience department from several smaller departments, including my own. The staff of the new department included from the beginning several distinguished neuroscientists like Hökfelt, Kjell Fuxe, Lars Olson, Gunnar Grant, Lars Gösta Elfvin, Staffan Cullheim, Krister Kristensson, Per Roland, and myself. As the founding chair of the department, it was a stimulating but not always an easy task to make the scientific cultures of these different areas interact. This coincided with a period of diminishing funding of research in Sweden, which meant that all departments received less funding. The Karolinska Institute nevertheless was favored, in that it received no less than around 40% of the total external national funding in life science and medicine, with the rest being shared among the universities in Uppsala, Lund, Göteborg, Umeå, and Linköping. Over the past 20 years, individual researchers now depend primarily on external funding—a situation quite different from earlier times, and this, it seems, has had a negative effect on the impact of Swedish science.

Selecting Nobel Laureates

I took part in the process of selecting Nobel laureates in Physiology or Medicine from 1986 to 2008 and chaired the Nobel committee for two years. This was a stimulating endeavor and allowed me to scrutinize a number of interesting studies in many different areas. The task was to identify important discoveries and determine who were the key individuals responsible (not more than three). The process was developed in 1901 (the first award), and has been important in maintaining a secure routine. For all nominations

being submitted (around 200 to 300 each year), a written preliminary report is provided, and for those that seem of particular interest, reports by different specialists are commissioned. Over several years, different reports are obtained that usually clarify the importance of a given discovery and that specify who are the main individuals responsible. The next question was to compare different prize constellations and which would be the most prize worthy in a given year. When comparing widely different areas, there can be no absolute justice, but the area chosen needs to represent a breakthrough. What has been critical to ascertain is that the laureates chosen for a given area are those who were instrumental in making the discovery. The Nobel Prizes awarded for the most part have been well received, and the 1901 strategy with written reports most certainly has been important in this context because it allows for going back to reports written years earlier. In contrast, most international prizes rely mostly on deliberations during committee meetings. The Nobel reports remain in secrecy for 50 years and then can be released, for example, to historians of science.

International Engagement

Since early on, I have had the privilege of interacting with colleagues in different parts of the world. An important early step was when I along with Paul Stein, Douglas Stuart, and Richard Herman co-organized a meeting of the neural control of locomotion in 1975 near Philadelphia. In this meeting, we, for maybe the first time, compared locomotion in vertebrates with that of invertebrates to look for common principles. This was at an early stage, but a creative interaction took place with the invertebrate model systems, like Crustaceans, Tritonia, locust, and cockroach, and on the vertebrate side, the experiments on humans and cats dominated but also a little bit of fish. Not surprisingly, we found that CPGs tended to be present in practically all model systems explored and similarly, in most cases, a sensory contribution was present helping to adapt the movements to the surrounding world. We continued to have a meeting every 10th year, in Stockholm in 1985, then Tuscon in 1995, and in Stockholm again in 2005. These meetings were stimulating, and useful for the field, and Rossignol, Forssberg, Wallén, El Manira, and Kiehn joined the organizing committee in different phases and combinations.

I always have had good interactions with different groups in North America over many years, and I was honored when SfN invited me to give the Grass Lecture in 1983, in which I talked about our studies on spinal organization of locomotion in the cat and also about our new findings in the lamprey. At that time, there were only two or three plenary lectures at SfN, and I was terrified to meet an audience 10 or 20 times bigger than I previously had experienced. The lecture was summarized in an article in *Science* in 1985. Afterward, I had the fortune to be asked to participate in many challenging events of this type.

I have had the pleasure of interacting with many different groups early in my career, including those with Stein in Saint Louis, Rossignol and Dubuc at the University of Montreal, Stuart in Tucson, Edgerton at UCLA, and Feldman working on the respiratory system at UCLA and invertebrate groups like those of Al Selverston (UCSD) and Eve Marder (Brandeis). I also was influenced and impressed by Eric Kandel's (Columbia) work on learning in *Aplysia* and of his ability to synthesize and integrate knowledge of the brain, an ability that he shares with Jean-Pierre Changeaux at Collège de France in Paris. Whereas Kandel received the Nobel Prize many years later (2000), this prize as yet has not been awarded to Changeaux. During later years, I have very much appreciated the interaction with Torsten Wiesel and his clear judgment in science and organization of research in a local and global perspective.

Over the years, in addition to collaborating with previous postdocs, I have interacted with many different groups like that of Francois Clarac in Marseille. We had a common EU grant and three of his PhD students (Jean-Yves Barthe, El Manira, and Vinay) joined my laboratory as postdocs. Vinay later made a stellar career in Marseille, working on mouse spinal cord, but sadly died unexpectedly at age 50 from an acute heart condition. Around 2000, I coordinated another EU grant on microcircuits (spinal cord, hippocampus, neocortex, and cerebellum) with Eric De Schutter, Jörn Hounsgaard, Eberhard Buhl, Lansner, and a young Henry Markram. In another important EU Select-and-Act Grant on the basal ganglia, we had a rewarding interaction with Paul Bolam, Hagai Bergman, and Ann Graybiel, and in yet another more robot-oriented grant, Lampetra, we worked with Paolo Dario in Pisa and with Auke Ijsbeert, Ekeberg, and Jean-Marie Cabelguen. Without a formal grant, there has been a close interaction with many, including Ansgar Buschges, who spent a year in our laboratory just before he was appointed as chair in Cologne.

FENS and IBRO

In 1990, I had taken on the task of organizing the European Neuroscience Association (ENA) annual meeting in Stockholm, with Per Andersen, then president of the society. This was demanding with limited and uncertain funding, but it worked. John Eccles and Ragnar Granit represented the Nobel laureates who provided a perspective on neuroscience, and Bert Sakmann, the year before he was awarded. Later, ENA was replaced by the Federation of European Neuroscience Societies (FENS), which organizes a pan-European meeting every second year, alternating with the meetings of the many national societies. I served FENS from 2010 to 2012 as president and promoted the establishment of a permanent FENS office in Brussels with an executive director and staff to work in the interest of the neuroscience community on many different levels. At the time, we also initiated a plan to develop one or

two permanent training sites in Europe (like Cold Spring Harbor), which was realized together with the International Brain Research Organization (IBRO) in Champalimaud (Lisbon) and Bordeaux in 2015. The interaction with Fotini Stylianopoulou as secretary general and Domnique Poulain as executive director during these two FENS years was joyful and productive.

I was subsequently elected as secretary general of IBRO from 2013 to 2015. The profile of IBRO is different from FENS; it has regional committees largely one for each continent and has an intention to promote neuroscience in middle- and low-income countries. One important aspect of this work is to promote training by PhD/postdoc courses in the different regions and another is to give short- and long-term travel grants and postdoc stipends. IBRO has an efficient secretariat led by Stephanie de la Rochefoucauld, which handles thousands of grant applications and interacts with all parts of the world. It has been interesting and rewarding to experience that many of these actions make a real difference and to try to further develop these activities.

The Need for Neuroinformatics—INCF and the Human Brain Projects

As I realized the importance of simulations in my interaction with Lansner and Hellgren, it also meant that I became engaged in trying to promote computational neuroscience and neuroinformatics. In the late 1990s, I became the Swedish representative to a group organized by the Organisation of Economic Co-operation and Development (OECD) in Paris and its Megascience Forum, which was tasked with exploring the possibilities of developing neuroinformatics on a global scale. At the NIH, it had been realized that databases should be important for neuroscience to facilitate retrieval of findings from different organizational levels, ranging from structural biology to microcircuits, systems, and behavior. Similarly, the importance of being able to develop detailed simulations was in focus. Rather than each country developing its own databases and infrastructure, the intention was that this should be a collaborative effort on a global scale. This OECD exploration resulted in a 2005 report calling for the formation of an International Neuroinformatics Coordinating Facility (INCF), which was endorsed by all ministers of research within OECD.

The next step was to actually form INCF, which happened in a telephone conference in August 2005 with seven member countries participating, and with me as the interim chair. The next question was where the secretariat should be located. The Swedish government at the time was interested in making a bid for a location in Stockholm. After a tight competition, an international high-level committee decided to locate the secretariat in Stockholm, at the Karolinska Institute, but with the KTH as a co-host of the secretariat. The Karolinska Institute offered space for the secretariat, and KTH offered a professorship in neuroinformatics and also provided

support from the KTH computer center. To build up the secretariat from scratch was a demanding task, with a staff of 12 people, mostly PhDs, who would mostly be program officers for the different projects. Jan Bjaalie was the first executive director, and did a good job in building up INCF, while I served as the founding chair of the board for the first seven years. INCF now has 18 member states that provide project funding; in addition, INCF receives funding as part of different international projects.

These activities also led to my involvement in the large EU flagship, the Human Brain Project (HBP), which started in 2013 and aims to develop new and more advanced software to allow detailed simulations extending from the subcellular level to synapses, neurons, microcircuits, and systems, and, ultimately, to behavior and cognition. This is a formidable ambition that will not be realized quickly. Nevertheless, I think it is critical to build up these important tools, because I am convinced that without detailed simulations, there will be no possibility to understand any complex process in the brain in terms of cells, synapses, and microcircuits. Unfortunately, this project has been plagued with a number of shortcomings and conflicts partially because of unrealistic expectations.

Last but Most Important: My Family

I met my wife Lena when we were both medical students in Göteborg. She specialized initially in infectious diseases, but then took up clinical virology and received her PhD in 1975, just before we moved to Stockholm. She changed over to the clinical virology department at the Karolinska hospital and after some years became its head. Subsequently, after fusion of some microbiology laboratories in the Stockholm area, she became the head of Clinical Microbiology in Stockholm, with millions of tests for bacteria and viruses each year.

We have two daughters: Pernilla, who is now a pediatrician and neuro-oncologist, and Katja, who is an architect and professor at the KTH. When they were in school, we had a nice companionship in that one of the daughters and I were responsible every second week for preparing the dinner, buying the food, and setting the menu of the week, and my wife with the other daughter were responsible in the alternating weeks. It was fun to plan together and take responsibility, and I think this was a nice thing to do and the children at the same time gained useful experience. It also meant that every second week, I was free in relation to conduct experiments and so forth. This was also a good way for my wife and I to split responsibilities, with both of us having a lot of demands on our time. For the children, it may have been more demanding to be with me, as I had rather often other things coming up. The children spent time in the lab or at the Marine Biology Station, where they sometimes helped. Since Pernilla was born, we have had a summerhouse, an old harbor pilot's house, on an island outside

Göteborg, which is scenic and provides a relaxing environment, allowing time for some sailing and snorkeling. It also has been good for writing and planning our next steps to take in science. We could not wish to have had a more enjoyable time with our children, and they are now the parents of a set of wonderful grandchildren. Although we both have had demanding careers, I owe very much to Lena for always being there to make things happen in a nice way and for keeping track of me, when I was overcommitted or just had made some of my many mistakes.

Conclusion

If we are to understand the operation of the brain in terms of cells, synapses, microcircuits, and beyond, we need to work with different approaches and select appropriate model systems. My ambition in this demanding endeavor has been to understand the detailed operation of the networks underlying the control of motion from the basic microcircuits in the spinal cord to the forebrain mechanisms underlying selection of motor programs. By using the lamprey as a model system, we have achieved this goal in many aspects. I believe we now have an integrated understanding of not only the neural bases of the locomotor networks but also the control of body orientation, tectal control, and forebrain mechanisms underlying selection of behavior, which taken together provides a more complete knowledge than in other vertebrate species. Moreover, we have shown that these circuits, including those in the forebrain, are conserved in evolutionary terms, which means that the basic design of these aspects of the motor system was conceived early in vertebrate development, some 560 million years ago.

Selected Bibliography

Work on Mammalian Motor System

Forssberg, H., and S. Grillner (1973). The locomotion of the acute spinal cat injected with Clonidine i.v. *Brain Res.* 50, 184–186.

Forssberg, H., S. Grillner, and J. Halbertsma (1980). The locomotion of the low spinal cat. I. Coordination within a hindlimb. *Acta Physiol Scand.* 108, 269–281.

Forssberg, H., S. Grillner, and S. Rossignol (1975). Phase dependent reflex during walking in chronic spinal cats. *Brain Res.* 85, 103–107.

Forssberg, H., S. Grillner, J. Halbertsma, and S. Rossignol (1980). The locomotion of the low spinal cat. II. Interlimb coordination. *Acta Physiol Scand.* 108, 283–295.

Georgopoulos, A.P., and S. Grillner (1989). Visumotor coordination in reaching and locomotion. *Science* 245, 1209–1210.

Grillner, S. (1972). The role of muscle stiffness in meeting the changing postural and locomotor requirements for force development by the ankle extensors. *Acta Physiol Scand.* 86, 92–108.

Grillner, S. (1973). Locomotion in the spinal cat. In *Control of Posture and Locomotion*, Stein R.B., Pearson K.G., Smith R.S., and Redford J.B., Eds., 515–535. New York: Plenum Press.

Grillner, S. (1975). Locomotion in vertebrates—Central mechanisms and reflex interaction. *Physiol Rev.* 55, 247–304.

Grillner, S. (2011). Human locomotor circuits conform. *Science* 334, 912–913.

Grillner, S., and T. Hongo (1972). Vestibulospinal effects on motoneurones and interneurones in the lumbosacral cord. In *Basic Aspects of Central Vestibular Mechanisms. Progress in Brain Research*, Vol. 37, A. Brodal and O. Pompeiano, Eds., 243–262.

Grillner, S., T. Hongo, and S. Lund (1971). Convergent effects on alpha motoneurones from the vestibulospinal tract and a pathway descending in the medial longitudinal fascicle. *Exp Brain Res.* 12, 457–479.

Grillner, S., J. Nilsson, and A. Thorstensson (1978). Intra-abdominal pressure changes during natural movements in man. *Acta Physiol Scand.* 103, 275–283.

Grillner, S., and S. Rossignol (1978). On the initiation of the swing phase of locomotion in chronic spinal cats. *Brain Res.* 146, 269–277.

Grillner, S., and M.L. Shik (1973). On the descending control of the lumbosacral spinal cord from the "mesencephalic locomotor region." *Acta Physiol Scand.* 87, 320–333.

Grillner S., and P. Zangger (1975). How detailed is the central pattern generation for locomotion? *Brain Res.* 88(2), 367–371.

Experiments on Spinal Locomotor Mechanisms in Dogfish

Grillner S. (1974). On the generation of locomotion in the spinal dogfish. *Exp Brain Res.* 20(5), 459–470.

Grillner, S., C. Perret, and P. Zangger (1976). Central generation of locomotion in the spinal dogfish. *Brain Res.* 109, 255–269.

Grillner, S., and P. Wallén (1982). On peripheral control mechanisms acting on the central pattern generators for swimming in the dogfish. *J Exp Biol.* 98, 1–22.

Experiments on Locomotor Networks in the Lamprey Spinal Cord

Alford, S., and S. Grillner (1991). The involvement of GABAB receptors and coupled G-proteins in spinal GABAergic presynaptic inhibition. *J Neurosci.* 11(12), 3718–3726.

Buchanan, J.T., and S. Grillner (1987). Newly identified 'glutamate interneurons' and their role in locomotion in the lamprey spinal cord. *Science* 236, 312–314.

Cangiano, L., and S. Grillner (2005). Mechanisms of rhythm generation in a spinal locomotor network deprived of crossed connections: The lamprey hemicord. *J Neurosci.* 25, 923–935.

Dale, N., and S. Grillner (1986). Dual-component synaptic potentials in the lamprey mediated by excitatory amino acid receptors. *J Neurosci.* 6(9), 2653–2661.

El Manira, A., J. Tegnér, and S. Grillner (1994). Calcium-dependent potassium channels play a critical role for burst termination in the locomotor network in lamprey. *J Neurophysiol.* 72(4), 1852–1861.

El Manira, A., J. Tegnér, and S. Grillner (1997). Locomotor-related presynaptic modulation of primary afferents in the lamprey. *Eur. J Neurosci.* 9, 696–705.

Grillner, S. (1985). Neurobiological bases of rhythmic motor acts in vertebrates. *Science* 228, 143–149.

Grillner, S. (1991). Recombination of motor pattern generators. Simple neuronal networks combine to produce complex versatile motor patterns. *Curr Biol.* 1(4), 231–233.

Grillner, S. (1996). Neural networks for vertebrate locomotion. *Scientific American*. January, 64–69.

Grillner, S., H. Markram, E. De Schutter, G. Silberberg, and F.E.N. LeBeau (2005). Microcircuits in action—from CPGs to neocortex. *TINS* 28(10), 525–533.

Grillner, S., and T. Matsushima (1991). The neural network underlying locomotion in lamprey-synaptic and cellular mechanisms. *Neuron.* 7, 1–15.

Grillner, S., and P. Wallén (1980). Does the central pattern generation for locomotion in the lamprey depend on glycine inhibition? *Acta Physiol Scand.* 110, 103–105.

Grillner, S., and P. Wallén (1985). Central pattern generators for locomotion with special reference to vertebrates. *Ann Rev Neurosci.* 8, 233–261.

Grillner, S., T. Williams, and P-C Lagerbäck (1984). The edgecell, a possible intraspinal mechanoreceptor. *Science* 223, 500–503.

Matsushima, T., and S. Grillner (1992). Neural mechanisms of intersegmental coordination in lamprey—Local excitability changes modify the phase coupling along the spinal cord. *J Neurophysiol.* 67, 373–388.

Schotland, J., O. Shupliakov, M. Wikström, L. Brodin, M. Srinivasan, Z. You, M. Herrera-Marschitz, W. Zhang, T. Hökfelt, and S. Grillner (1995). Control of lamprey locomotor neurons by colocalized monoamine transmitters. *Nature.* 374, 266–268.

Wallén, P., K. Carlsson, A. Liljeborg, and S. Grillner (1988). Three-dimensional reconstruction of neurons in the lamprey spinal cord in whole-mount, using a confocal laser scanning microscope. *J Neurosc Meth.* 24, 91–100.

Central Canal Cells and the pH Control of Motor Activity

Jalalvand, E., B. Robertson, P. Wallén, and S. Grillner (2016). Ciliated neurons lining the central canal sense both fluid movements and pH through ASIC3. *Nature Com.* 7, 10002.

Jalalvand, E., B. Robertson, P. Wallén, R.H. Hill, and S. Grillner (2014). Laterally projecting cerebrospinal fluid-contacting cells in the lamprey spinal cord are of two distinct types. *J Comp Neurol.* 522(8), 1753–1768.

Jalalvand, E., B. Robertson, H. Tostivint, P., and S. Grillner (2016). The spinal cord has an intrinsic system for the control of pH. *Curr Biol.* doi:10.1016/j.cub.2016. 03.048.

Simulation of Locomotor Activity in Lamprey

Ekeberg, Ö., P. Wallén, A. Lansner, H. Tråvén, L. Brodin, and S. Grillner (1991). A computer based model for realistic simulations of neural networks. I. The single neuron and synaptic interaction. *Biol Cybern.* 65, 81–90.

Hellgren Kotaleski, J., A. Lansner, and S. Grillner (1999). Neural mechanisms potentially contributing to the intersegmental phase lag in lamprey. II Hemisegmental oscillations produced by mutually coupled excitatory neurons. *Biol Cybern.* 81, 299–315.

Kozlov, A., M. Huss, A. Lansner, J. Hellgren Kotaleski, and S. Grillner (2009). Simple cellular and network control principles govern complex patterns of motor behavior. *Proc Natl Acad Sci USA.* 106, 20027–20032.

Kozlov, A.K., A.A. Kardamakis, J. Hellgren Kotaleski, and S. Grillner (2014). Gating of steering signals through phasic modulation of reticulospinal neurons during locomotion. *Proc Natl Acad Sci USA.*111, 3591–3596.

Tråvén, H.G.C., L. Brodin, A. Lansner, Ö. Ekeberg, P. Wallén, and S. Grillner (1993). Computer simulations of NMDA and non-NMDA mediated synaptic drive—sensory and supraspinal modulation of neurons and small networks. *J Neurophysiol.* 70(2), 695–709.

The Lamprey Brainstem and Midbrain Control of Body Orientation and Steering

Asteriti, S., S. Grillner, and L. Cangiano. A Cambrian origin for vertebrate rods. *Elife*. 4,. e07166. doi: 10.7554/eLife.07166

Deliagina, T.G., G.N. Orlovsky, S. Grillner, and P. Wallén (1992). Vestibular control of swimming in lamprey. II. Characteristics of spatial sensitivity of reticulospinal neurons. *Exp. Brain Res.* 90, 489–498.

Grillner, S., and R. Dubuc (1988). Control of locomotion in vertebrates: Spinal and supraspinal mechanisms. In *Advances in Neurology*, Vol. 47, *Functional Recovery in Neurological Disease*, Waxman, S.G., Ed., 425–453. New York: Raven Press.

Kardamakis, A.A., K. Saitoh, and S. Grillner (2015). Tectal microcircuit generating visual selection commands on gaze-controlling neurons. *Proc Natl Acad Sci USA.* 112(15), E1956–E1965.

Lamprey Basal Ganglia and Habenulae

El Manira, A., M.A. Pombal, and S. Grillner (1997). Diencephalic projection to reticulospinal neurons involved in the initiation of locomotion in adult lampreys *Lampetra fluviatilis*. *J Comp Neurol.* 389, 603–616.

Pombal, M.A., A. El Manira, and S. Grillner (1997). Afferents of the lamprey striatum with special reference to the dopaminergic system: A combined tracing and immunohistochemical study. *J Comp Neurol.* 386, 71–91.

Stephenson-Jones, M., J. Ericsson, B. Robertson, and S. Grillner (2012). Evolution of the basal ganglia; dual-output pathways conserved throughout vertebrate phylogeny. *J Comp Neurol.* 520, 2957–2973.

Stephenson-Jones, M., O. Floros, B. Robertson, and S. Grillner (2012). Evolutionary conservation of the habenular nuclei and their circuitry controlling the dopamine and 5-hydroxytryptophan (5-HT) systems. *Proc Natl Acad Sci USA.* 109, 164–173.

Stephenson-Jones, M., A.A. Kardamakis, B. Robertson, and S. Grillner (2013). Independent circuits in the basal ganglia for the evaluation and selection of actions. *Proc Natl Acad Sci USA.* 110(38), E3670–E3679.

Stephenson-Jones, M., E. Samuelsson, J. Ericsson, B. Robertson, and S. Grillner (2011). Evolutionary conservation of the basal ganglia as a common vertebrate mechanism for action selection. *Curr Biol.* 21, 1081–1091.

Pallial/Cortical Control of Movements in Lamprey—Projection Patterns Conserved

Ocaña, F.M., S. M. Suryanarayana, K. Saitoh, A.A. Kardamakis, L. Capantini, B. Robertson, and S. Grillner (2015). The lamprey pallium provides a blueprint of the mammalian motor projections from cortex. *Curr Biol.* 25(4), 413–423.

The Respiratory Network in Lamprey

Cinelli, E., B. Robertson, D. Mutolo, S. Grillner, T. Pantaleo, and F. Bongianni (2013). Neuronal mechanisms of respiratory pattern generation are evolutionary conserved. *J Neurosci.* 33, 9104–9012.

Cinelli, E., D. Mutolo, B. Robertson, M. Contini, T. Pantaleo, and F. Bongianni (2014). GABAergic and glycinergic inputs modulate rythmogenic mechanisms in the lamprey respiratory network. *J Physiol.* 592, 1823–1838.

Other Works Mentioned in the Text

Bethe, A. (1899). Die locomotion des Haifisches (Scyllium) und ihre Beziehungen zu den einzelnen Gehirntheilen und zum Labyrinth. *Arch. Gesamte Physiol.* 76, 470–493.

Brown, T.G. (1911). The intrinsic factors in the act of progression in the mammal. *Proc R Soc London Ser.* B 84, 308–319.

Gray, J. (1968). *Animal Locomotion.* London: Weidenfeld and Nicolson.

Gray, J. and H.W. Lissmann (1946). Further observations on the effect of de-afferentation on the locomotory activity of amphibian limbs. *J Exp Biol.* 23, 121–132.

Holst, E. von (1935). Ûber den Process der zentralnervösen Koordination. Pfluegers *Arch Gesamte Physiol Menschen Tiere.* 236, 149–158.

Jankowska, J., M.G. Jukes, S. Lund, and A. Lundberg (1967). The effect of DOPA on the spinal cord. 6. Half-centre organization of interneurons transmitting effects from the flexor reflex afferents. *Acta Physiol Scand.* 70, 389–402.

Lundberg, A. (1969). Reflex control of stepping. The Nansen Memorial Lecture V. Oslo: Universitetsforlaget, 1–42.

Sherrington, C.S. (1906). *The Integrative Action of the Nervous System.* New Haven, CT. Yale Univ Press.

Sherrington, C.S. (1910). Flexion-reflex of the limb, crossed extension reflex and reflex stopping and standing. *J Physiol London.* 40, 28–121.

Steiner, I. (1886). Über das centralnervensystem den grünen Eidechse, neben weiteren untersuchungen über das Haifischer. *Sitzber K Preuss Acad Wiss.* 32, 539–543.