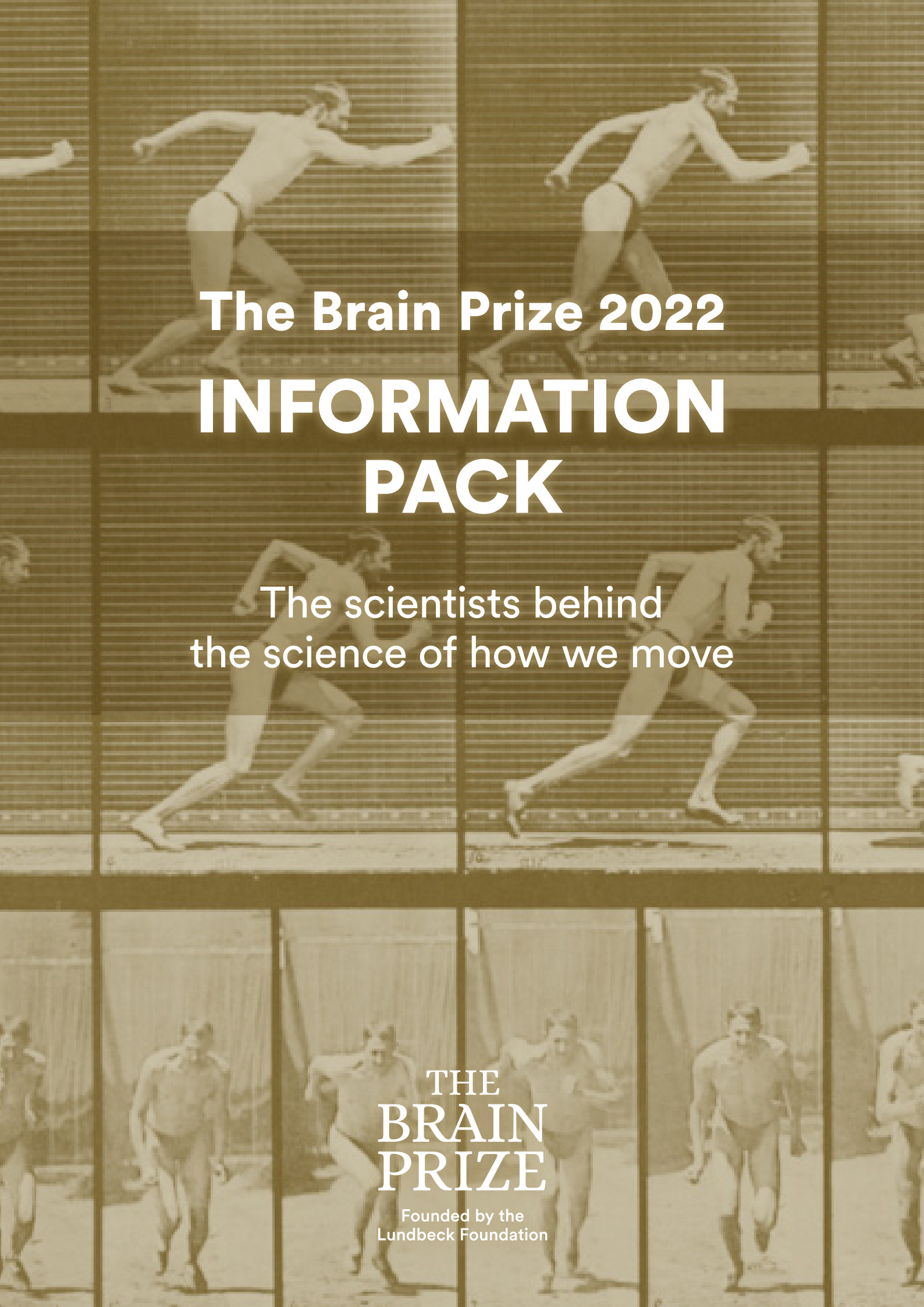


The Brain Prize 2022

INFORMATION PACK

The scientists behind the science of how we move

THE BRAIN PRIZE

Founded by the Lundbeck Foundation

Pioneering research into the neuronal circuits that control movement has been recognized with the award of The Brain Prize 2022

LUNDBECK FOUNDATION

All our interactions with the world depend on our ability to move. Understanding how the nervous system generates movement is a fundamental goal of neuroscience and is at the heart of devising new strategies for the restoration of movement following injury or disease. An international group of three neuroscientists have revolutionized our understanding of the cell types and circuits that control how we move. Theirs is a remarkable discovery story in fundamental neuroscience that highlights the need and paves the way for cell type-specific diagnostics and interventions in disorders of movement. For this, the three neuroscientists are receiving the world's largest prize for brain research – The Brain Prize – which is awarded annually by the Lundbeck Foundation.

This year The Brain Prize worth DKK 10 million (€1.3 million) is awarded to:

Silvia Arber (Switzerland)
Martyn Goulding (USA/NZ)
Ole Kiehn (Denmark)

Professor Richard Morris, Chair of The Brain Prize Selection Committee, explains the reasoning behind the award:

"There is nothing more fundamental to animal life than movement. Behaviour is expressed by movement of the whole animal or parts of its body, and a core role of the central nervous system is to successfully produce such coordinated movement. Defining the circuits and the roles of neuronal classes that produce movements is critical; both for a basic understanding of how the nervous system works and, as importantly, for understanding what goes wrong in the various medical conditions affecting normal movement. Silvia Arber, Martyn Goulding and Ole Kiehn and have revolutionized our understanding of the fundamental cells and circuits underlying mammalian body movement and have defined the importance of these elements in health and disease"

Front cover: Consecutive images of a man running.
From Eadweard Muybridge's, Animal Locomotion, 1887

About the Brain Prize

Scope

The Brain Prize is the world's largest neuroscience research prize, and it is awarded each year by the Lundbeck Foundation. The Brain Prize recognises highly original and influential advances in any area of brain research, from basic neuroscience to applied clinical research. Recipients of The Brain Prize may be of any nationality and work in any country in the world. Since it was first awarded in 2011 The Brain Prize has been awarded to 41 scientists from 9 different countries. Read more about The Brain Prize laureates here. Brain Prize recipients are presented with their award by His Royal Highness, The Crown Prince of Denmark, at a ceremony in the Danish capital, Copenhagen.

How Brain Prize recipients are selected

Only candidates who are nominated by others will be considered for The Brain Prize. Each year, the Lundbeck Foundation receives many outstanding nominations from all over the world. Recipients of The Brain Prize are chosen from the pool of nominees by The Brain Prize selection committee which consists of 9 leading neuroscientists from diverse disciplines within neuroscience. More information about the nomination and selection process, and the selection committee can be found here.

Purpose

The Brain Prize is first and foremost a celebration of outstanding science and outstanding scientists. Following the award of The Brain Prize, recipients engage in a series of seminars, lectures, and conferences, organised by the Lundbeck Foundation. These activities celebrate the achievements of The Brain Prize winners and help raise awareness of their work and their field amongst the international neuroscience community. The Brain Prize is also used as a platform to engage with and educate the public about the importance of brain research, its challenges, and breakthroughs. The Brain Prize also serves to highlight the Lundbeck Foundation's vision of making Denmark a leading neuroscience nation.

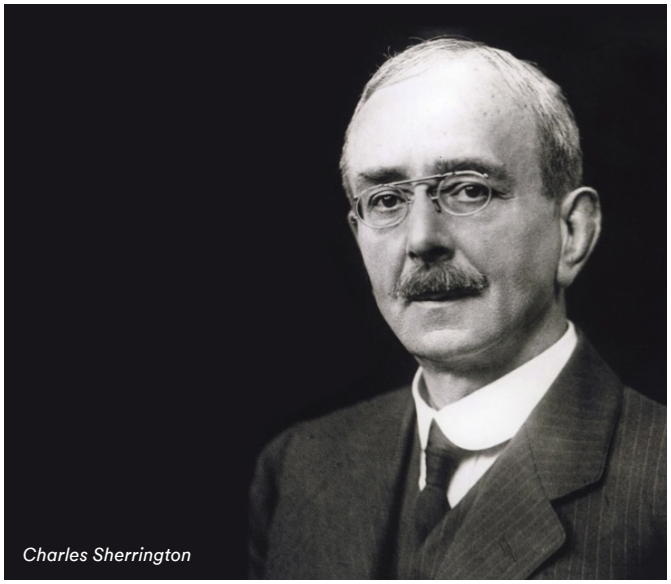
Brain Prize Winners 2022: Commentary

The neuronal circuits that control movement

Martin Meyer
Director of The Brain Prize, The Lundbeck Foundation

**"All mankind can do is move things...
whether whispering a syllable or felling a forest"**

This quote from Charles Sherrington, who, along with Edgar Adrian, received the Nobel Prize in 1932 for their work on motor reflexes, is a reminder of the fact that all our interactions with the world are through movement. It also highlights the enormous repertoire of movements that we are capable of, from the seemingly simple such as walking and talking (or whispering) to the highly skilled, such as playing the piano. While skilled movements may require practice and concentration, most movements are made effortlessly. We can therefore perhaps be forgiven for taking our ability to move for granted. However, when our ability to move is compromised through injury or during disease it is devastating and a stark reminder of how fundamental movement is for life.



Charles Sherrington

Understanding the circuits that produce movement has long been at the heart of understanding how nervous systems produce behaviour. It also lays the foundation for devising strategies for restoration of movement after injury or disease. However, the circuits that control movement are widely distributed throughout the brain and spinal cord and they are composed of many different neuronal cell types, each with characteristic functional properties and patterns of connectivity. The different cell types are not discernible just by looking at the brain or spinal cord and the problem is compounded by the fact the different cell types are intermingled. Classical approaches to studying the brain, such as electrical recordings of individual neurons, pharmacological manipulations or lesioning of different brain areas have provided important insights into the neural control of movement. However, they are limited in that they cannot be used to reproducibly identify, interrogate, and manipulate the individual neuronal cell types involved.

The opportunity to overcome these limitations came from studies of nervous system development which revealed that cell types within the spinal cord could be distinguished from one another by the pattern of developmentally important genes that they expressed. These studies laid the groundwork for this year's Brain Prize winners, Silvia Arber, Martyn Goulding and Ole Kiehn to characterize and analyse the roles of identified cell types by combining molecular genetic with classical approaches in mice. Working in parallel and sometimes together, Arber, Kiehn and Goulding have used these techniques to describe in unprecedented detail the cells and circuits that control diverse aspects of the movement repertoire.

Spinal circuits that set the rhythm and pattern of locomotion

Locomotion is the ability of animals to move from one place to another and the rhythm and pattern (gait) of locomotion in vertebrates is controlled by networks of neurons within the spinal cord. Arber, Kiehn and Goulding have identified neuronal components of spinal circuitry and defined how each of them contribute to distinct aspects of locomotion. For instance, Kiehn and Goulding have identified different classes of neuron that control the speed of locomotion, the alternating pattern of limb movements used during slower gaits such as walking, or the rhythmic alternation of flexor and extensor muscle activity that lift and extend the limbs during locomotion. (Figure 1)

Locomotion is rhythmic and balanced - we do not, under normal circumstances, constantly adjust our pace nor move limbs on one side of the body in a manner that is very different from those on the other. Martyn Goulding has identified a neuronal cell type that balances the strength and duration of activity on either side of the spinal cord and ensures that this activity has a stable rhythm. These neurons are therefore likely to be crucial for producing a balanced and fluid gait. Finally, Silvia Arber has revealed the overall organization of spinal neurons that connect to motor neurons and in the course of this work, she has identified neurons that are essential for ensuring postural stability and coordination of fore- and hindlimbs during walking. Arber, Kiehn and Goulding have thus identified components of the mammalian spinal network that ensure that when we move from A to B we can do so at different speeds, and with different gaits that are stable, balanced, and rhythmic.

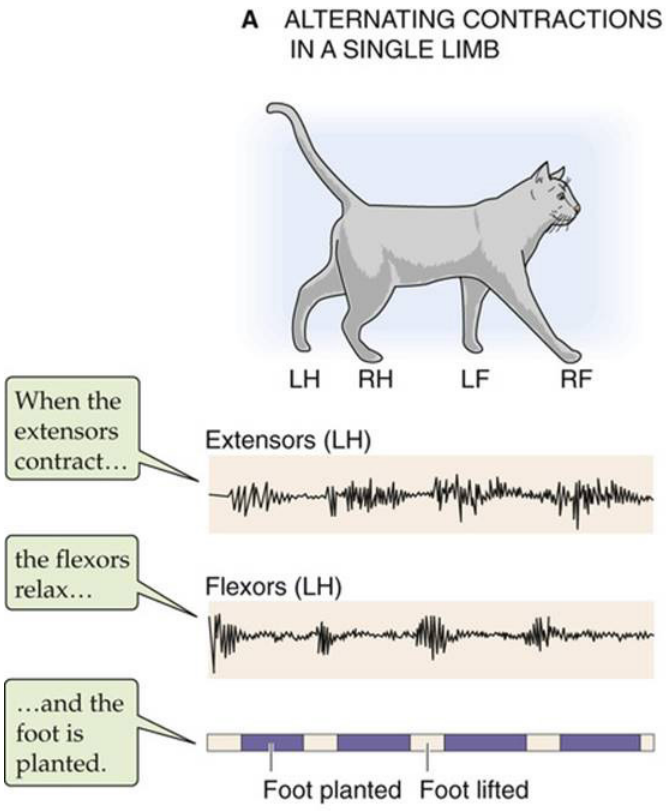


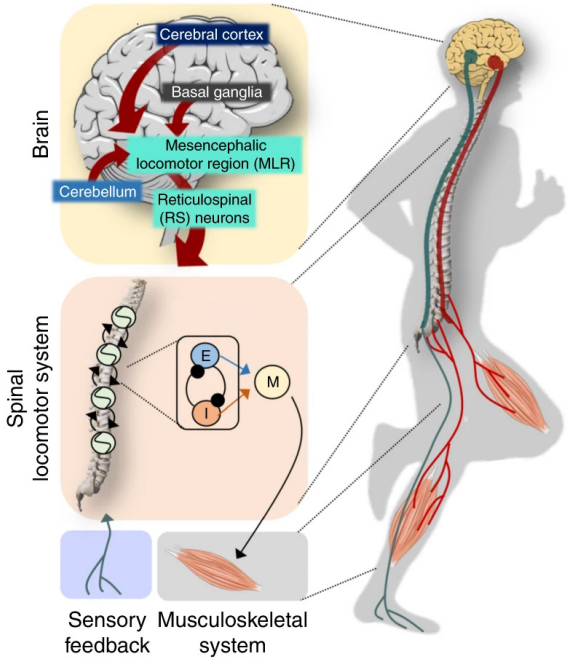
Figure 1. *Rhythmic patterns of motor neuron activity that control the extensor and flexor muscles of a single limb. When extensor muscles are activated the flexor muscles are relaxed and the foot is extended (planted). The opposite happens when the limb is lifted. Image adapted from Medical Physiology, 3rd Edition 2017 by Walter Boron and Emile Boulpaep, Elsevier.*

Descending control of movement

Circuits within the spinal cord control the pattern and rhythm of locomotion but they cannot generate movement without descending input from the brain (Figure 2). The most striking illustration of this point is that patients with complete spinal cord injuries exhibit paralysis of the body below the site of injury. Using cell and site-specific activation Arber and Kiehn have revealed dedicated neuronal populations in the brainstem that generate signals for the initiation, termination, speed, and direction of locomotion. They have also defined areas of the midbrain and forebrain that recruit the different brainstem populations to direct goal directed behaviours such as foraging for food or escaping predators. However, locomotion represents just a small part of an animal's movement repertoire. For example, mice use dextrous movements of their forelimbs for grasping and handling food. Work from Silvia Arber's lab has shown that there are areas of the brainstem that are dedicated to controlling forelimb movement and that within the brainstem there are neurons that are dedicated to specific phases of forelimb movements such as reaching or food handling. The work of Kiehn and Arber has thus demonstrated the exquisite organization of brainstem command pathways to the spinal cord at the cellular level. Acting like a neuronal switchboard that directs plans for movement from mid- and forebrain structures to the spinal cord, it controls diverse aspects of movement from locomotion to the delicate and dextrous movements of the limbs.

Regulation of movement by the senses

Modulation of the motor system by the senses is crucial for adapting our movements according to ongoing changes in the environment. In recent work Goulding has identified neurons in the spinal cord that serve as an interface between sensory and motor systems. These neurons receive input from sensory neurons in the skin that convey information about light touch stimuli and ablating them markedly reduces the behavioural responses of mice to light touch and dramatically increases the frequency of foot slips when mice are walking along a beam. These neurons are therefore necessary for generating compensatory movements in response to changes in the terrain that are sensed by the skin of the feet. How we move isn't just modulated by sensory information that we receive from the external environment. It is also constantly updated by sensory input from the proprioceptive system which conveys information from our own muscles, joints and tendons which tell us about how our limbs are moving and where they are in space. Silvia Arber has revealed mechanisms that determine how proprioceptive sensory neurons and motor neurons involved in the knee jerk reflex are precisely wired up during development. Martyn Goulding has also identified neurons in the spinal cord that filter proprioceptive information that arrives in the spinal cord from the flexor muscles of the hindlimbs. When these neuronal filters are absent, mice develop a duck-like gait where flexion of the limbs is exaggerated. These findings suggest that by gating proprioceptive sensory information, these neurons prevent abnormal flexor muscle reflexes that would disrupt the ongoing locomotor program, thereby securing the smooth rhythmic limb movements of a fluid walking gait.



Overview of the motor system. Plans for movement are generated in areas of the brain such as the cerebral cortex. Plans for movement are relayed to the spinal cord by different regions within the brainstem such as the Mesencephalic Locomotor Region and the Reticulospinal system. Descending commands control the activity of circuits in the spinal cord consisting of excitatory (E) and inhibitory (I) interneurons which control the activity of motor neurons (M) that control muscle tension. Spinal circuits are modulated by sensory feedback from receptors in the skin, muscles, joints, and tendons. Image adapted from Dutta, S., Parihar, A., Khanna, A. et al. Programmable coupled oscillators for synchronized locomotion. Nat Commun 10, 3299 (2019). https://doi.org/10.1038/s41467-019-11198-6.

New strategies for restoring movement after injury or disease

By revealing how identified populations of cell types in the brainstem and spinal cord contribute to specific aspects of movement, Arber, Kiehn and Goulding have highlighted the need and paved the way for cell type-specific diagnostics and interventions in movement disorders. For example, amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that results in progressive loss of motor neurons which continues until the ability to eat, speak, move, and finally to breathe is lost. Ole Kiehn has identified a specific spinal neuron population that is affected in ALS before motor neurons begin to die, thereby identifying a new target for intervention therapy. Any design of rehabilitation strategies after spinal cord injury must build on an understanding of which populations of neurons to target. Silvia Arber has shown that input to the injured spinal cord from proprioceptive sensory neurons in the muscle is essential for the remodelling of spinal circuits following injury. This discovery points to the need for rehabilitation strategies or stimulation that specifically targets these proprioceptive neurons. Ole Kiehn has also identified circuit mechanisms in the spinal cord that contribute to spasticity – devastating and involuntary muscle contractions following spinal cord injury. This work may open the door to developing new pharmacological treatments for ameliorating these muscle spasms. Finally, the identification of neurons in the brainstem that can control the initiation and termination of movement suggests the potential use of targeted stimulation strategies to improve movement in Parkinson's disease.

As a result of the work of Silvia Arber, Martyn Goulding and Ole Kiehn our understanding of the neuronal networks that control movement has advanced considerably since Sherrington won his Nobel Prize nearly 100 years ago. There are still many questions to answer but thanks to this year's Brain Prize winners, we are many steps closer to understanding how we move.

Defining cells, circuits and movements

David McLean

Associate Professor of Neurobiology and Neuroscience at Northwestern University

Our intentions are manifest through actions, which in turn permeate our descriptive language. Our mind races when we are excited. We lose our grip when we are frustrated. We jump for joy when we're happy. When we're sad, we feel downtrodden. In fact, actions are so linked to the expression of life they make inanimate objects seem empathetic. The plastic bag scene in Sam Mendes' film 'American Beauty' famously demonstrates that humans can be moved by things that move.

In his book 'I of the Vortex', Rudolfo Llinas argues that the nervous system owes its existence to the need to move around. And as animals evolved better navigating capacities through time, the increased computational capacity of the nervous system enabled more complex consideration of actions – moving from reactive to proactive. So, by exploring how brain cells and their synaptic connections form circuits that generate movements, we gain access to neural blueprints guiding the evolution of circuits for thoughts and feelings. To reveal what moves us figuratively, we can reveal what moves us literally.

Locomotion, the ability to translate from point A to point B, is a common and essential component of navigation. Whether point B is toward a mate or nutrition, or away from a predator or obstacle, animals have evolved ways to steer and propel with varying degrees of urgency and precision. Critically, locomotion is generated by regions of the vertebrate nervous system that have changed the least over time – the brainstem and spinal cord. This means fundamental insights into human motor control in both health and disease can be revealed by studying animal models that provide better experimental access.

Interest in the neural circuitry responsible for vertebrate locomotion has a relatively long history. In particular, studies of mammalian spinal circuits at the turn of the 20th century enabled Nobel prize winning discoveries by Charles Sherrington and his trainee John Eccles on the function of neurons and the way they synaptically excite and inhibit one another. To put this in perspective, trying to understand the origins of dementia without the concept of neurons and synapses would be like trying to understand the origins of social media without the concept of the internet.

Then, as now, the goal was to provide a foundation for a functional understanding by first assembling comprehensive wiring diagrams – like reverse engineering a complex piece of machinery by first detailing the components and their connections. Sherrington's studies of the reciprocal innervation of antagonistic motor groups served as the first conceptual framework to understand the coordination of mammalian locomotion – namely how flexor and extensor muscles in the limbs alternate along and across the body during walking.

Sherrington believed that sensory stimuli were critical to generate locomotion, with excitatory and inhibitory afferent circuitry forming a chain of reflex pathways. However, in 1911 Sherrington's trainee T. Graham Brown published the first proof that locomotion can be generated by neural circuits within the spinal cord in the absence of sensory stimuli and the brain. This meant that even simple behaviors like locomotion are not just reactive – they are proactive, but can be adapted by reactions. With this key observation, the hunt for the identity of central circuits responsible for controlling and coordinating mammalian locomotion was on. And with it, a search for the origins of neural dynamics in the brain.

The period of discovery in the mid to late 20th century was characterized by the development of pharmacological, immunocytochemical and electrophysiological approaches and new vertebrate model systems. Anders Lundberg, who connects to Sherrington through his advisor Ragnar Granit, championed Graham Brown's work decades earlier and with his trainees Elzbieta Jankowska and Hans Hultborn explored the descending and sensory control of spinal locomotor circuits in cats. Another Lundberg trainee, Sten Grillner, moved from cats to lampreys, which promised a

simpler and more robust preparation. Eccles trainee Donald Faber also moved to goldfish for the same reason. Studies of early developing animals were also motivated by better experimental access to simpler locomotor circuits, including Lynn Landmesser's work in chicks, Alan Roberts work in frog tadpoles, and Jack Feldman and Norio Kudo's efforts developing neonatal rodent preparations.

The idea was that circuit designs of fundamental importance should be reflected in as many animals and ages as possible. However, there were limits to discovery. The spinal cord lacks the layered structure of the cerebellum and cortex or the nuclear structure of the brainstem, which makes repeated sampling and circuit mapping more challenging. The distributed organization of the spinal cord also made it impossible to test the validity of any emerging wiring diagrams without a means to predictably alter circuit function.

This all changed around the turn of the 21st century with the discovery of conserved biochemical and genetic codes regulating the development and specification of spinal neurons by Thomas Jessell and colleagues. Remarkably, the relatively haphazard distribution of neurons in the adult spinal cord emerged from an orderly spatial gradient that was most obvious during early development. Transcription factors could be used to define particular classes of spinal neurons and to map their synaptic connectivity in neonates and adults. This enabled the application of emerging molecular genetic tools to label, activate or silence specific populations, finally providing ways in which existing theories could be tested and new theories created. The neural basis of locomotion and behavior was finally within reach.

The requirement for genetic access winnowed the pool of popular model systems. However, previous circuit work in frog tadpoles, goldfish and lampreys supported new examinations of molecularly defined circuits in transgenic zebrafish, pioneered by Faber trainee Joseph Fetcho in younger fish and Grillner trainee Abdel El Manira in older ones. Similarly, work in canines, felines and rodents served as a foundation for examinations of molecularly defined spinal circuits in transgenic mice. The ability to compile and compare organizational features in different species is key – expecting a single model system to define principles is like expecting a single data point to define a trend.

The Prize winners, Martyn Goulding from the USA, Silvia Arber from Switzerland, and Ole Kiehn from Denmark, have led the charge in locomotor circuit discovery in the mammalian spinal cord. Significant conceptual advances have always been fueled by technical ones and the Prize winners highly productive and complementary research programs fuse modern and traditional methods to explain the origins of locomotion – answering questions that were first posed a century ago. Their work is characterized by a holistic view of locomotion, striving to define principles of circuit operation through the lenses of development and evolution, with a scholarly appreciation for the history of the field and the vision to lead it forward.

Martyn Goulding's early work defined how the differentiation of the spinal cord was driven by a cascade of transcription factors. He was the first to recognize the power of using molecular genetics to 'break' spinal circuits to assess their function. His development of intersectional genetic strategies to label and perturb discrete populations of neurons set the standard for the field and enabled experiments in neonates and adults, where the basics of circuit organization appear to be consistent. Among his many accomplishments, Goulding's efforts revealed the identity of spinal inhibitory circuits responsible for flexor-extensor alternation during locomotion, as predicted by Graham-Brown. More recently, Goulding has shifted his focus to the functional logic of spinal sensory circuits, specifically how movements are shaped by light touch and itch – familiar ground for Sherrington.

Silvia Arber's early work with Jessell defined central molecular pathways controlling the specification and connectivity of distinct neuronal subpopulations in the knee-jerk reflex – again, Sherrington's back yard. In her own lab, she pioneered viral tracing methods and intersectional genetic strategies to map reflex circuit assembly, spinal premotor interneuron connectivity, and bidirectional interactions between neurons in the spinal cord and brainstem. Her substantial body of work has defined spatial and temporal principles linking motor planning centers, brainstem hubs and spinal executive circuits, providing key insights into how connectivity prefigures action selection and behavioral integration. Arber continues to push further upstream to better understand how behaviors are orchestrated.

Ole Kiehn's early work was with Hultborn in cats but he moved to neonatal rodents in his own lab. His lab was instrumental in developing in vitro recording approaches that enabled cellular and circuit level analyses during 'fictive' locomotion in rodents. He also identified regions of the lumbar spinal cord responsible for locomotion and their sensitivity to neuromodulators. Kiehn's lab embraced emerging molecular tools early on, at first employing and later on developing a

combination of genetic and optical technologies to interrogate spinal locomotor circuits. Collectively, his remarkable efforts identified populations of spinal neurons responsible for activating locomotion, demonstrated the minimum circuit required for flexor-extensor alternation during locomotion, mapped circuits for coordinating locomotor activity across the body, and revealed modular circuits for gait selection as mice move over a range of speeds to explore and evade.

The fundamental basic neuroscience carried out by the Prize winners is also leading to translational breakthroughs. For instance, Ole Kiehn's work on spinal inhibitory interneurons has revealed their contribution to symptoms of ALS. Silvia Arber's work on spinal reflexes is leading to new ways to promote functional recovery after spinal cord injury. More broadly, the neuronal diversity reported by their collective work highlights the need for cell-type specific interventions in the designing more effective therapies for motor disorders.

As Sherrington illustrates, innovators and pioneers are not defined by what they may have gotten wrong. Instead, they are defined by their ability not only to raise the bar, but also to raise an entire conceptual framework for the next generation to explore. Healthy connections between neurons may move us forward, but as history reports it is the ones between mentors and trainees that ultimately move the field forward. Each of the Prize winners reflects these high standards and they have given current and future mentors a great deal to run with.

Autobiographies of the 2022 Brain Prize winners

Silvia Arber

Biozentrum University of Basel &
Friedrich Miescher Institute, Basel, Switzerland

I consider neuroscience to be the last big frontier in biology, allowing researchers to explore totally uncharted territory. I live this passion together with my research team at the Biozentrum of the University of Basel and at the Friedrich Miescher Institute (FMI) in Basel, Switzerland - two institutions that have been important corner stones throughout my scientific career.

It is an enormous privilege to live in present times where we can uncover organizational and functional principles of the nervous system with unprecedented precision and speed. The tremendous cellular diversity in the nervous system has always been a big fascination for me and I thrive to understand how diverse cell types communicate with each other to bring about function. My experience has been that diving deep into the secrets of the nervous system always brings about more clarity once one uncovers the principles that underly its organization. In particular, the high degree of synaptic specificity between neuronal cell types and how this specificity in circuitry aligns with and brings about behavioral function is a recurring theme in my research. The concept of uncovering anatomical circuit specificity to probe the importance of these patterns for behavior has been very fruitful. Studying these questions in the motor system has been the most logical entry point, as its components orchestrate all of our many diverse behaviors. In addition to providing deep insight into how the motor system executes and learns diverse movements, we hope that this approach will also contribute to understanding circuit deficits in diseases of the motor system such as Parkinson's and ultimately allow to design targeted interventions to improve movement in patients.

My studies of Biology at the Biozentrum of the University of Basel, Switzerland (1987-1991) were concluded with my master thesis (1991) on a cell biological topic in the laboratory of Pico Caroni, a junior group leader at the FMI in Basel, Switzerland. Being exposed to research in neuroscience for the first time convinced me to pursue this avenue for my future research. I subsequently continued in Pico Caroni's laboratory as a PhD student (1992-1995) undertaking a screen at the neuro-muscular junction, the synaptic intersection between motor neurons and muscles. This screen took me in different directions including the field of muscle differentiation, neuronal growth and unexpectedly cardiology with the generation of the first mouse model for dilated cardiomyopathy. This experience taught me that scientific discovery is unpredictable and that keeping your eyes open for the unexpected to constantly adjust priorities as new results come along is an essential ingredient in science. For me, one of the most wonderful attributes of being a researcher is the unexpected nature of discovery. Pico Caroni remained my mentor and compass after my PhD thesis and until today, being also highly instrumental in building up the Basel Neuroscience community on the topic of Circuit Neuroscience over many years, and allowing me to thrive in an extremely exciting environment during my independent career.

Driven by my desire to understand cellular diversity in the nervous system, I joined the laboratory of Thomas

Jessell at Columbia University for my postdoctoral work (1996-2000). His laboratory had made fundamental discoveries on how cell types in the spinal cord acquire diverse fates during development, based on genetic programs of combinatorial transcription factor expression. I wanted to employ these insights to try to determine whether transcriptional programs in neuronal subtypes might also control how they grow axons to innervate specific targets and integrate to connect into specific circuit modules. I found that members of the ETS transcription factor family are expressed in subpopulations of motor and sensory neurons, and that the expression of these transcriptional programs was dependent on factors provided by target tissues. Thus, neurons acquire their fates progressively, with early cell intrinsic programs transitioning to a phase in which also target-derived cues can influence the expression of transcriptional programs and hence neuronal differentiation. My experience in Tom Jessell's laboratory was another very formative step in my career. The concept that developmentally expressed genetic programs lay the foundation for the generation of neuronal subtypes and their subsequent differentiation is still deeply embedded in my thinking today. In my view, the personal history of a neuron including its developmental maturation and transitioning into specific programs of plasticity in the adult are core components of how the nervous system functions, a concept that many neuroscientists working on function do not embrace.

In April 2000, I started to build up my independent research group in Basel, Switzerland, based on a joint appointment between the Biozentrum and the FMI. This arrangement that I still hold and value today allowed me to integrate into two outstanding research institutions and to live my dream of working together with trainees at many stages of education in many different settings. It allows my research group to bridge between the Biozentrum, a university research institution also involved in teaching students, and the FMI, an institution focusing on high-level biomedical research with major financial support from the pharmaceutical company Novartis. It is this special environment that allowed me to develop my research program for now more than twenty years, has supported my technological developments and also given me the full freedom to venture into new territories and expand my horizon without any boundaries as I will outline below. The trust they have put into me and my team is phenomenal. None of what follows would also have been possible without the highly dedicated and passionate team of coworkers I have had the pleasure to work with. Acknowledging their individual contributions here would not do justice to the fact that our progress has truly been a continuous team achievement throughout the last more than twenty years.

Arber Lab retreat 2018 in the Swiss Alps (Engadin).

Since I started my laboratory in 2000, our efforts have been on unraveling principles of how the motor system is organized and functions. Our early years were dedicated to shedding light on the molecular components involved in the development of specific sensory-motor reflex arcs, better known by laypeople as the knee-jerk-reflex. In this system, one can study a circuit with essentially just two types of components, motor neurons and muscle spindle sensory neurons, wiring up literally every muscle of the body into a specific circuit loop in which sensory neurons provide feedback about muscle contraction to motor neurons. We clarified the role of ETS and Runx transcription factor signaling in development of motor and sensory neurons, and also found that specific cell surface molecules downstream of transcription factors can be mediators of developing appropriate patterns of synaptic specificity.

Transition to a second phase of research in my laboratory was triggered by a revolutionary development in virus technology which turned out to be a real game changer for our research. The laboratory of Ed Callaway published a genetically modified rabies virus, allowing to trace circuits retrogradely with restriction to monosynaptically connected neurons. We adjusted this technique to visualize neurons with direct synaptic connections to motor neurons in the spinal cord. We made use of the exquisite topographical arrangement of motor neurons into so-called motor neuron pools. A motor neuron pool harbors motor neurons innervating one muscle in the periphery, allowing us to selectively map the input to motor neurons with distinct function in the control of movement. We visu-

alized the distribution of spinal neurons connected to motor neurons regulating the contraction of extensor or flexor muscles, active during stance or swing phases of walking respectively; or to motor neurons with postural function of the trunk. Interestingly, we revealed distinct organizations of these so-called premotor interneurons for functionally different motor neuron pools, suggesting that there are anatomical correlates of differential functions discernable in the spinal cord. Also striking in this analysis was the huge number and large 3-dimensional distribution of premotor spinal neurons along the rostro-caudal axis, demonstrating the importance of studying motor output organization as a systems level question rather than restricted to a small part of the spinal cord. Unlike for many sensory systems, where the precise organization of first synapses into the nervous system was long understood, the analogous knowledge in the motor system at the last step out presynaptic to motor neurons was only approachable with precision through the development of these wonderful viral tools.

The same technological breakthrough also allowed us to venture beyond the spinal cord in subsequent work, where we asked about the origin, organizational logic and function of central commands for different body movements from the brain. We focused our attention on the brainstem, a key switchboard between upper motor planning centers and executive circuits in the spinal cord. We reasoned that insight into this part of the brain will allow us not only to unravel central descending command lines to the spinal cord orchestrating diverse body movements such as locomotion or skilled forelimb movements, but also be a stepping stone to understand how these brainstem neurons integrate information about movement and participate in action selection. In a first series of experiments, we visualized the distribution of brainstem neurons connected to forelimb- or hindlimb innervating motor neurons. We argued that should there be anatomical correlates of function, we might observe differences in communication pathways, since the two extremities are involved in distinct motor programs. This approach indeed was highly successful. We found that brainstem neurons connecting to motor neurons can be subdivided into three categories, by whether they communicate with one of the two types of motor neurons, or both. We subsequently probed this anatomical specificity model in the most recent set of studies, again enabled by wonderful recently developed methods including optogenetics, recording of neuronal activity in freely moving mice deep in the brain, and precise behavioral tracking.

We found that specific classes of brainstem neurons are at the core of regulating important parameters of skilled forelimb movement, primed by our anatomical visualization of brainstem neurons with connections to forelimb innervating motor neurons. On the other hand, brainstem neurons transmitting information along the rostro-caudal axis of the spinal cord have roles in full body movements including regulating important parameters of locomotion (e.g. speed) or body extension such as used in rearing. Together, our work provides evidence for exquisite spatial and synaptic organization of brainstem neurons and their roles in regulating coordination, precision and coherence of diverse body movements. In future work, important questions to address will include how identified brainstem populations are regulated by diverse upstream centers including basal ganglia and cortex, and how they communicate with each other, to be selected for the right type of movement at the right time and vigor to execute and possibly learn movements.

A small body of work in my laboratory has begun to apply our insights and technologies to how the nervous system reacts to injury or disease. Here, we focus on how specific neuronal populations react to or are important components in injury or disease situations, with the goal to leverage these insights for possible interventions. We found that proprioceptive sensory feedback is absolutely essential to drive functional recovery after incomplete spinal cord injury. It does so by acting below injury and aids the connectivity of descending detour circuits including specific brainstem pathways to promote the process of functional recovery. Going forward, we hope that some of our most recent work in the brainstem will also be useful to understand circuit mechanisms in the progression of neurodegenerative disorders such as Parkinson's disease, and possibly provide application to ameliorate motor symptoms. For example, rather than applying deep brain stimulation to entire brain regions, more rational approaches targeting subpopulations with known properties to restore or maintain selective functions might in the future be more successful. More generally, I am convinced that interventions in disease and injury will need to take into account the high level of synaptic specificity with which neuronal circuits are connected, both locally and at the systems level.

I would like to end this account of my scientific journey on a few words about my upbringing and events that influenced me during this time. I am extremely grateful to have experienced a wonderful and carefree childhood with my parents Antonia and Werner Arber, as well as my six years younger sister Caroline,

who today leads a research group on CAR-T therapy development in Lausanne, Switzerland and is an MD. After a one year stay at the age of two in Berkeley US, where my father was on a sabbatical, I grew up in Basel where I went to school until entering my University studies. I learned to enjoy nature, hiking, skiing and music early on together with my family, all of which I still value tremendously today. These activities allow me to recharge batteries but they also often bring to me the best ideas for my own science. One might say I also learned to be a researcher during my childhood: I frequently went to the laboratory with my father as a child, enjoying counting bacterial colonies and other activities. When I was ten years old, my father was awarded the Nobel Prize for the discovery of restriction enzymes. While this changed his life in terms of being busier, it never changed him, his modesty and honesty, and I was and am deeply impressed by this. My upbringing in this wonderful caring family taught me to stay grounded and to live a passionate and intense life.

Summer holidays in Flims (1977), Switzerland with my parents and my sister Caroline.

Ole Kiehn

Department of Neuroscience,
University of Copenhagen, Denmark
& Department of Neuroscience,
Karolinska Institutet, Sweden

I was born and raised in Nakskov on Lolland, an island south of Zealand. My father's family were craftsmen and came from Germany to Denmark in the late 19th century. My mother's family came from Jutland where my grandfather, a primary school teacher, ended up with my grandmother on Lolland, where he became the head of one of the elementary schools in Nakskov. During my upbringing Nakskov was a proud provincial town, with a shipyard and a sugar factory. My father worked as an engineer at the shipyard, while my mother took care of my sisters and me.

My father Kaj and mother Kirsten in the fifties.

Starting in the elementary school I was a slow learner but caught up – with support from my parents and tutoring from my grandfather – and went to high school where we had a team of amazing young teachers that were very inspiring and ignited broad interests in knowledge and nurtured curiosity.

I started medicine in Copenhagen in 1977. I had considered biochemistry and biology or comparative literature. I ended up with medicine because it covered everything from the molecules to systems and functions. The first years lived up to my expectations and I was happy. When the clinical part started, I realized that I had difficulties imagining my-self as a medical doctor so I looked for an exit strategy. I decided to get involved in research. My interest in the brain had emerged because my girlfriend at the time had her first severe epileptic seizure. I contacted Hans Hultborn who was a newly appointed professor from Sweden at the Institute for Neurophysiology in Copenhagen. He was working with motor control in the cat spinal cord and together with Jørn Hounsgaard they had just started to look at spinal network or neuron properties that could explain the generation of persistent motor activity. Experiments in the cat spinal cord had a long tradition from the time of Sherrington, Eccles and Lundberg for studies of motor control in mammals. I became part of the team and exactly on midnight when I turned 25 we showed that motor neurons can express plateau potentials, converting short-lasting inputs into persistent output. This was a significant discovery that I was so fortunate to be part of. It was the beginning of my scientific career. I graduated from medicine a few years later and I was lucky enough to get a research stipend from the University of Copenhagen and therefore I never went into the clinic. We continued with the plateau potentials and described their neuromodulation, the ionic mechanisms and looked for their presence in the intact animals, and my doctoral thesis in 1990 was all about this.

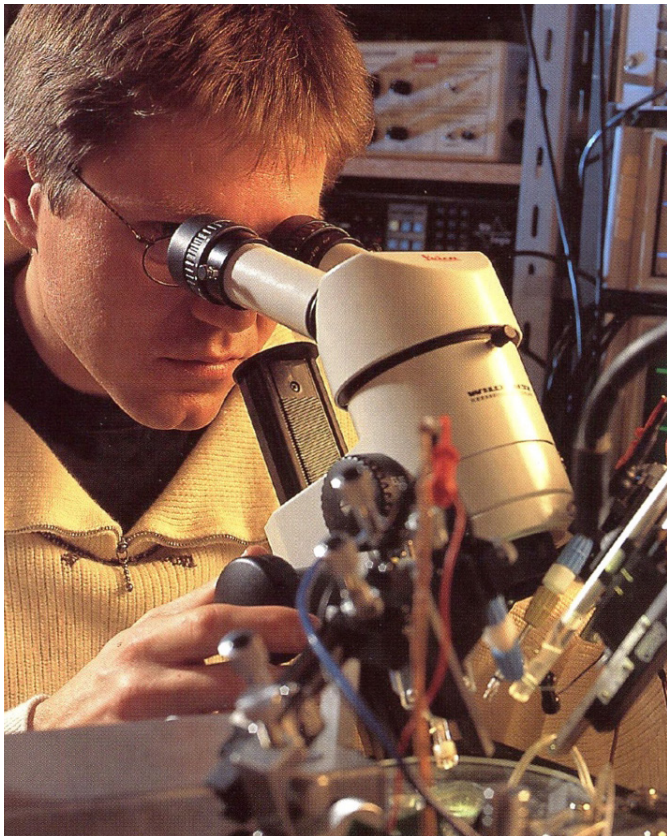
My sisters, Anne Mette and Susanne, and I, 1984.

The spinal cord had become my scientific base and motor control my research focus. In my opinion movement is so important because it is through the execution of movements that we express and sense most of our existence. Understanding the mechanisms for its generation is critical for understanding how the nervous system works at a fundamental level and can provide a basis for better treatment of motor symptoms in the diseased brain.

I went on to a postdoc at Cornell University working with Ron Harris-Warrick on the stomatogastric ganglion. With its 30 neurons it was tractable in terms of understanding how neuronal circuits generate behavior and has been a model system for understanding neural circuits. I studied neuromodulation of plateau properties and I learned to appreciate the power of knowing the identity of each neuron in the network.

In 1990 I started my lab in Copenhagen. My interest was in neural networks and how they generate behavior. I would focus on locomotion in mammals. Locomotion is one of the most fundamental movements and used in so many of life's daily activities. It was well-known that the timing, the rhythm, and the pattern – left-right and flexor-extensor coordination - is generated by interneuron circuits in the spinal cord itself. The spinal cord was therefore a good place to start. Details of spinal networks involved in swimming was known from the much simpler nervous system in lamprey – spearheaded by Sten Grillner and colleagues and in the tadpole by work from Allan Roberts, Keith Sillar and others. However, in mammals the organization of the spinal locomotor networks were mostly unknown. I decided that a different system than the cat spinal cord would be needed if we were to understand the spinal locomotor networks in mammals. Norio Kudo's lab in Japan and Jack Feldman's lab in US had shown that the isolated spinal cord from newborn rats could be kept alive ex vivo for a long time and produce a rhythmic motor output resembling locomotion. The preparation was brilliant for studying the mammalian locomotor network and in 1992 I went to visit Kudo's lab to learn the technique and bring it back to Copenhagen. With PhD student Ole Kjærulff we first identified the ventral cord as the site of the locomotor network. To get further with the network analysis we needed to be able to record from interneurons. However, with conventional sharp glass electrodes it was impossible because of the small size of neurons in the rat spinal cord. Around 1994 postdoc Morten Raastad and I introduced 'blind' whole cell recordings in the spinal cord which allowed us to target neurons of any size. In excitement we performed massive recordings from interneurons and motor neurons and characterized their cellular properties and synaptic modulation during locomotor activity. But except for motor neurons all the neurons were unidentified. We knew the location of the recorded neurons in the cord but nothing more. Unlike many parts of the brain the cord has no nuclear structure; neurons of different types are all intermingled in the same location. I decided that we needed to record from identified neurons and my first choice was commissural neurons; with their axons crossing to the other side, they could repeatedly be identified. By nature, they must also be involved in left-right coordination.

The idea was that they could then serve as a first handle or probe to the rest of the network. From around 1996 and over the coming many years we anatomically characterized the commissural neuron network in the rodent spinal cord, determined their transmitter content, determined their relationship to rhythmic muscle activity, and their direct or indirect projections onto motor neurons, and showed that left-right coordination circuits contain multiple pathways for alternating and synchronous movements. Many fantastic postdocs and students, including Simon Butt, Ole Kjærulff, and Kathy Quinlan, participated in this immense work.



Looking for interneurons in the spinal cord, 1995.

In 1995 I was the lucky recipient of the Hallas Møller research stipend paying my salary for 5 years and in 1997 I became an Associate Professor at Department of Physiology in Copenhagen. Despite eventually having my permanent position in Copenhagen I was restless and looked around for other possibilities. In 1998 I was offered a professorship in Oslo but eventually I took up a position as group leader at Karolinska Institutet, Stockholm, in the Department of Neuroscience where I later became a full professor in 2004.

A lesson learned from studies of small sized networks - like the stomatogastric ganglion - was that activation or inactivation of neurons could reveal their function in the network. To obtain similar loss-of-functions or gain-of-functions in large mammalian networks was only possible if activity in many neurons of the same type could be selectively changed. This would require that groups of neurons could be identified, e.g. by expression of specific molecular markers or transmitters, and that activity-controlling actuators could be expressed specifically in these neurons. It should turn out that the motor networks in the spinal cord would lend itself beautifully to such approaches. Techniques to genetically ablate or in other way inactivate neuronal activity was developed in the early 2000. At the same time neuroscientists – including Tom Jessell, Martyn Goulding and others – had discovered a developmental genetic code in the mouse spinal cord that assigned specific molecular markers to neurons in the region where we knew the locomotor network was localized. The time was ripe to converge the effort using more classical motor neurophysiology, anatomy and behavioral studies with the field of mouse genetic to test the role of molecularly defined neurons in locomotion. In this new era we embarked on an extensive series of experiments using this approach that allowed us to identify key elements of the mammalian locomotor network. This momentum coincided with Martyn Goulding, Joel Glover and Ron Harris Warrick all being on sabbatical in my new lab at KI.

Firstly, I wanted to try to target the rhythm generating network. We knew from the lamprey and tadpole swimming network that rhythm generating networks most likely were composed of excitatory and ipsilateral projecting neurons but it could not be shown in a direct way. In the mouse spinal cord so-called V2a neurons was one of the genetically defined groups of neurons that anatomically fulfilled these criteria. In collaboration with Kamal Sharma's lab ´we showed that the V2a neurons contributed to left-right coordination but not the rhythm. Although it was possible to fit the V2a population into our proposed scheme of left-right alternation it was a bit of a disappointment that we could not show any contribution to rhythm generation. I decided that we should create a mouse-line that expressed the light activated channel, channelrhodopsin, in all excitatory neurons in the spinal cord so we could test the hypothesis directly. These where very early days in optogenetic mice production but senior scientists Lotta Borgius and Peter Löw successfully produced a mouse line and with PhD student Martin Hägglund we could for the first time demonstrate that glutamatergic cells in the cord are responsible for rhythm generation and also later that the rhythm generation circuit has a modular organization. It was a nice step forward and using a suite of molecular techniques and electrophysiology we eventually were able to link the rhythm generation to a smaller group of excitatory neurons genetically defined as Shox 2 neurons in a terrific collaboration with Jessell and Arber labs and carried through by postdoc Kimberly Dougherty in my lab.

With intersectional mouse genetics we also discovered that the multiple left-right circuits that we had revealed electrophysiologically, had a functional meaning. Using a mouse line generated by Allessandra Pierani, postdocs Adolfo Talpalar and Julien Bouvier showed that two subgroups of the so-called V0 neurons are required for left-right limb alternation at different speeds of locomotion. These molecularly distinct sets of commissural neurons constrain the expression of the alternating gaits, walk and trot shown by postdoc Carmelo Bellardita. It was a major feat for me to see that the circuit outline we knew from our electrophysiology studies found direct support from V0 neuron specific ablation experiments.

In other series of experiments we showed directly that the reciprocally connected inhibitory Ia interneurons - first characterized in cat spinal cord - are core elements of the flexor-extensor coordinating spinal circuits.

The work on left-right coordinating and the rhythm generation circuitries could be knitted together with work from other labs including Martyn Goulding's on flexor extensor circuitries and together it provided a common solution to how the key aspects of spinal locomotor output is generated in mammals.

In the mid 2010s I started to focus on brainstem circuits controlling the expression of locomotion. The existence and need for brainstem command pathways controlling the function of spinal locomotor network was well-known but as in the spinal cord, neurons in

the brainstem are intermingled and circuits had been probed with methods with little cellular and low regional specificity. Using optogenetics experiments we provided the first direct evidence that glutamatergic neurons in the lower brainstem provide an initiating signal to activate the spinal locomotor networks. In the hunt for defining these excitatory pathways in detail we - Julien Bouvier, Vittorio Caggiano and Roberto Leiras among others - discovered a new excitatory command pathway constituted of molecularly defined 'V2a stop neurons' in the medulla whose activation caused an intended stop. We - Caggiano, Leiras and Haizea Goni Erro and others - also targeted the locomotor start region in the brainstem and showed that two separated glutamatergic nuclei in the midbrain form command pathways that start locomotion and encode speed in complementary ways. In separate experiments postdoc Jared Cregg uncovered the organization of brainstem circuits that are essential for controlling turning or directionality of locomotion. These experiments therefore contributed to the understanding of the organization of fundamental command pathways essential for start, stop and turning of locomotion. They were initiated at Karolinska Institutet and has continued after I moved the majority of my lab back to Copenhagen in 2017 to the newly formed Department of Neuroscience which was made possible by a long-lasting grant from the Novo Nordisk foundation. I have retained my affiliation with Karolinska Institutet.

I have always had a strong focus on basic neuroscience. I love this view and I hope that we in the future will be able to use the motor pathways to understand even better how higher brain functions - that use the movement as expression - come about. Recently I have used our knowledge about the motor circuits to investigate the involvement of spinal neurons to development of ALS (with assistant professor Ilary Allodi), define new strategies to repair motor function after spinal cord injury (with assistant professor Carmelo Bellardita) or to promote movement and locomotion after Parkinson's Disease (with postdoc Debora Masini and others). It is very satisfying to see that basic neuroscience discoveries may lead to improvement of treatment for brain diseases or trauma to the brain even it is only in its infancy.

The work I have described would not have been possible without the many students, postdocs and senior researchers in my lab. Although I have not been able to mention all in this short telling of the story, I am indebted to all. Also warm thanks to many collaborators around the world.

Movement has been at the core of my life. When I look back on my upbringing it has been a journey from a non-academic to an academic life. In pursuing my goals, I have moved several times and most people that have worked with me have moved from different places in the world.

This diversity has been an enrichment to my life. So has my wife. In 2006 I was married to Inger Houbak, who is an art historian and painter. Our worklives are very different but these differences have widened my horizon and broadened my mind. I am very grateful for this and for the constant support I receive from her and from her true kind-heartedness.

My wife, Inger Houbak, and I 2022.

Martyn Goulding

Salk Institute for Biological Sciences, La Jolla, USA
& a New Zealand citizen

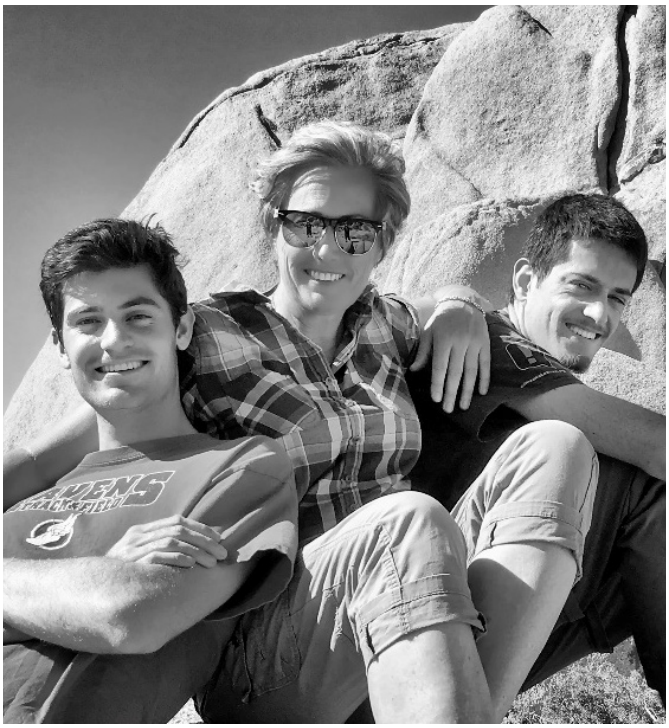
I had the great fortune of growing up in New Zealand, a progressive society that provided me with educational opportunities I may not have had elsewhere. My mother was a paraplegic who had contracted polio during the worldwide 1948 epidemic and she was left to raise her three children when my father left at a young age. Importantly, she understood the value of education and pushed for my younger brother and I to attend Hamilton Boys High School with its strong focus on academics. This is where I first developed a strong interest in science and biology in particular. From an early age there was a strong expectation that I would attend university, and I was first in the family to do so at the University of Auckland. My initial career aim was medicine, but my real passion was science and discovery. I remember my early experiences in the lab being a mixture of frustration when things didn't work and elation when they did. There were many times that I would leave the lab late in the evening having had an experiment fail, but I would always return the next day brimming with new ideas and enthusiasm. My mentor Ray Ralph's hands-off approach facilitated my development as a young scientist, allowing me to follow my ideas and fail in order to succeed. Others in the Cell Biology Department, particularly Dick Bellamy, Richard Gardner and Dave Lane, were also incredibly supportive.

Choosing where and with whom you do your 'postdoc' is a key step in a scientist's career. I decided to move away from the field I had done my graduate work in, namely cancer biology, and take on the challenge of vertebrate development in the lab of Peter Gruss at the Max Planck Institute in Göttingen, Germany. It was 1988, and efforts to understand the genetic programs regulating embryonic development were just beginning. I was particularly excited by the work being undertaken in Peter's lab cloning and characterizing the mouse homologues of transcription factors that pattern the fruit fly embryo. One of the reasons I chose to shift fields came from reading the seminal 1987 paper by Mario Capecchi and Kirk Thomas describing homologous recombination in mouse embryonic stem cells. I realized that this technique would usher in the era of gene targeting whereby it be possible to inactivate specific genes in the mouse and then assess their function in development. Upon arriving in Göttingen, I was rapidly integrated into the humming environment where the lights stayed on until well after midnight. Peter's lab was both intellectually stimulating and resource rich. Excited by the science and realizing this was a unique opportunity, I threw all my energy into my work. Yolanda my wife, who accompanied me and had put her career in graphic design on hold, was incredibly supportive. Given my very limited grasp of the German language, she was also my invaluable interpreter.

Working at the cryostat as a postdoc in the lab of Peter Gruss, Göttingen (1990).

My project involved cloning and characterizing the Pax3 gene. Pax3 was particularly intriguing in so far as its expression in the developing nervous system defined a territory in the embryonic spinal cord that subdivided it into dorsal and ventral halves. Pax6 and Pax7 also displayed dorsoventrally restricted patterns of expression in the developing spinal cord. This expression revealed for the first time the partitioning of the mammalian embryo into distinct dorsal and ventral territories, and it suggested a role for the Pax genes in patterning cell types along the dorsoventral axis. In 1990 Peter provided me with the opportunity to speak at a small exclusive meeting of the leading figures in developmental neuroscience and neurogenetics in Geneva Switzerland where I presented my results on Pax3. It was at this meeting that I first came into contact with Andrew Lumsden and we quickly got to discussing the work of Henny van Straaten, Tom Jessell and Jane Dodd on the role of the notochord in specifying ventral cell types in the developing spinal cord, and in particular the floorplate and motor neurons. My interactions with Andrew and the close collaboration that developed from it marked a turning point in my career with an ever-increasing focus on understanding the specification of cell types in the spinal cord, a quest that I would continue in my own lab at the Salk Institute. With Peter's support, Andrew and I then embarked on a series of experimental manipulations in the chick that demonstrated signal from the notochord and floor plate regulated Pax gene expression, not only in the spinal cord but also in the adjacent mesoderm tissue that forms the skin, muscle and vertebral column. Another key moment was an invitation in 1991 to speak at a conference in Leeds. It was there that I heard Chris Doe speak about his elegant work on identifying neuroblasts in the ventral nerve cord of Drosophila. I was struck by his description of the stereotypical spatial organization of genetically-defined neurons. This was a eureka moment for me, as it suggested that a similar organization might exist in the developing spinal cord where cell types with specific molecular identities might arise at different dorsoventral positions.

Very little was known about the neuronal cell types in the embryonic spinal cord in the early 1990's when I was completing my postdoc, so after establishing my lab at the Salk Institute as assistant professor, I set out to characterize a number of the interneuron populations that occupy discrete dorsoventral locations in the embryonic cord. My initial focus was on cells that express En1 and Evx1. However, at that time the available toolsets for these transcription factors only labeled the nucleus and cell body, and thus provided limited information about the neuronal cell type.



My family, Yolanda, Wynton and Callum, relaxing after hiking and rock climbing in Joshua Tree, California (2016).

Moreover, there was no way to lineage trace these cells. At the time I was grappling with this problem, John Thomas, a Salk colleague working in Drosophila, came up with the clever strategy of fusing sequences encoding the microtubule associate protein tau to lacZ, which resulted in transportation of the tau-b-gal protein along the axon so that the axonal processes could be visualized. We took advantage of this and used homologous recombination to generate a knockin mouse where the tau-lacZ gene was under the control of En1 regulatory sequences. This approach turned out to be a game changer, as we could now visualize the morphology of these En1+ or V1 neurons. By characterizing the morphology of these neurons we were able to make the bold prediction that En1+ V1 interneurons differentiate into two inhibitory interneuron cell types previously characterized in the adult cat spinal cord, namely Renshaw cells and Ia inhibitory interneurons. More importantly, this prediction and its later validation, provided the first demonstration of a lineal relationship between molecularly-identified interneuron cell types in the embryonic spinal cord and physiologically-defined interneurons in the adult spinal cord.

Hanging out with Andrew Lumsden while visiting him in London following my move to the Salk (1993).

In dissecting the developmental programs that generate spinal neurons in the cord, I was increasingly drawn to asking questions about their function, particularly with respect to locomotion. This was predicated on the idea that the developmental programs controlling neuronal specification and circuit formation could be leveraged to functionally dissect neural circuits using the molecular genetic approaches available in mice, something that Silvia Arber was also pursuing in the Jessell lab. I believed that the embryonic factors that regulate cell fate and connectivity could be used to mark and characterize specific populations of neurons, but more importantly, selectively manipulate them with a high degree of precision.

I also thought that this approach would build a bridge between molecular and classic systems neuroscience approaches, thereby providing new ways to study the spinal motor circuitry. It would also allow us to piggyback on the many seminal findings that had been made in the cat spinal cord by the likes of Eccles, Lundberg Jankowska and others. I was also influenced by the elegant probing of the locomotor central pattern generator (CPG) by Sten Grillner and Ole Kiehn, which was beginning to provide a conceptual framework for understanding the core spinal circuitry for locomotion. With all this in mind, I decided to visit Ole in Copenhagen to tell him about our findings and discuss harnessing the power of mouse genetics to explore the cellular nature of the locomotor CPG in mice. Thus began a new exciting chapter of discovery for both of us, which was supported by a Human Frontiers Science Program Grant. This collaboration gained further momentum when in the summer of 2001 I spent three months in Ole's lab, that had just moved to the Karolinska. This is where our experiments in the neonatal spinal cord were started. Our experiments were punctuated by stimulating discussions with Ron-Harris Warrick who was undertaking a sabbatical with Ole, and with Sten, each with their unique and insightful perspectives. My lab had previously shown that mice lacking the Pax6 gene exhibited a selective loss of the V1 INs. This gave us an entry point into assessing the role that this cardinal class of interneuron plays in generating the locomotor rhythm, and it resulted in a collaborative paper published in Nature showing the V1 neurons regulate the cadence of the locomotor rhythm. This study together with our earlier function analysis of the V0 interneurons laid a foundation for defining the cellular organization and logic for the mammalian locomotor CPG.

With Peter Gruss when he was visiting the Salk (circa 2003).

A beach walk with Ole in Encinitas when he was visiting California (2016).

While we pursued the functional characterization of the V2b and V3 interneurons, Ole in collaboration with Kamal Sharma turned his attention to a second population of excitatory neurons, the V2a interneurons. Their studies revealed a key role for the V2a neurons in rhythmic burst production and in left-right coordination. We on the other hand were able to show that the V3 interneurons are required for generating symmetrical locomotor rhythm across the spinal cord. Our analysis of the V2b INs was more complicated with a number if puzzling twists. Initially we thought that these cells might control flexor-extensor alternation, the key axis of motor coordination for limbed locomotion, however, they didn't seem to do much on their own. It was only when we inactivated them together with the V1 INs that flexor-extensor alternation was disrupted. This led to the surprising conclusion that Ia inhibitory interneurons in the spinal cord have a dual developmental origin, and as such are a developmentally diverse population. These findings have allowed us to speculate on the evolutionary changes in the swimming CPG that may have given rise to an alternating flexor-extensor rhythm and the eventual colonization of land by vertebrates.

With my graduate mentor Ray Ralph at following the Hood Lecture at my alma mater, the University of Auckland, New Zealand (2017).

I was then drawn to the question of the roles these neurons make to locomotion in a more natural context. However, the problem we faced was that the genes such as En1 are expressed in other areas of the CNS, including regions of the hindbrain that are necessary for breathing and motor learning. In order to specifically interrogate their role in locomotion in awake behaving mice we needed to come up with a way of selectively targeting the V1 and V2b neurons in the cord. This was no mean feat and was further complicated by their columnar organization in the spinal cord. To overcome this, we a turned to an intersectional approach, and it was up to Olivier Britz, a postdoc in my lab to solve this issue. His efforts were herculean and the outcome by no means certain, but they paved the way for a number of seminal studies by my lab and other labs that have provided key insights into the function of many of the interneuron cell types found in the cord populations. In a groundbreaking study published in eLife, Olivier was able to show that the V1 and V2b neurons have specific role in controlling flexor-extensor movements in awake behaving mice, with the V1 INs preferentially gating flexion, while the V2bs gate extension.

More recently my interest has turned to the dorsal spinal cord and the role that neurons in the dorsal horn play in both somatosensation and in transmitting sensory information to the core locomotor CPG networks in the ventral spinal cord that we have begun to define. This is a work in progress, but already have been able to define roles for a number of these dorsal interneurons in locomotion and in reflexive and corrective movements that are engaged when animals are moving and encountering new environments with their associated hazards. Two examples come to mind. First the RORa neurons that serve as a nexus for integrating light touch information form the periphery, but are also innervated by descending motor control pathways. This shows that these cells do not just simply relay sensory information to the motor system, but instead integrate information from multiple streams to modulate ongoing movement. The second was our demonstration that inhibitory RORb INs in the dorsal horn ensure fluid walking movements by gating proprioceptive inputs to the spinal cord.

Looking back, I have been exceptionally lucky in my family life with a wonderful and supportive wife, and two great sons that each have their own interests and passions. With regards to my career, I have always had the great fortune of being around others who supported me, first as a student and postdoc, then subsequently as a faculty member at the Salk where my MNL colleagues, Chris Kintner, Greg Lemke and John

Thomas backed me and believed in me. Of equal importance have been the many great collaborators that I have worked with. Andrew Lumsden, Eric Frank, Paco Alvarez, Ed Callaway, Qiufu Ma and Tom Jessell all deserve mention. Most importantly, it has been the great postdocs and students in my lab that have driven the science that we have done. Finally, all of this would not have been possible without my long-term lab manager Tommie, who has accompanied me throughout this scientific journey. There are also many others, too many to name, but they know who they are. My biggest role model has been my mum, who despite not being able to walk (or possibly due to it) showed determination and grit throughout her life and never gave up. It is these qualities that have helped me succeed in science, along with a lot of luck and help along the way.

My mother Dorothy who lost her ability to walk due to polio, seated in her wheelchair.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