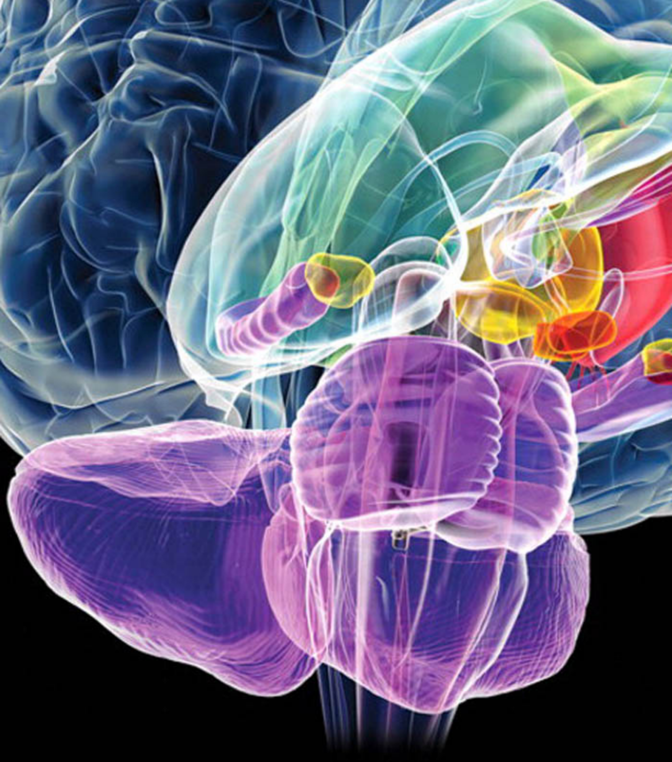

CEREBELLUM

The Brain for an Implicit Self

The Cerebellum

This page intentionally left blank

The Cerebellum:
Brain for an Implicit Self

Masao Ito

Vice President, Publisher: Tim Moore
Associate Publisher and Director of Marketing: Amy Neidlinger
Acquisitions Editor: Russ Hall
Editorial Assistant: Pamela Boland
Senior Marketing Manager: Julie Phifer
Assistant Marketing Manager: Megan Graue
Cover Designer: Alan Clements
Managing Editor: Kristy Hart
Project Editor: Jovana San Nicolas-Shirley
Copy Editor: Charles Hutchinson
Proofreader: Kathy Ruiz
Indexer: Angela Martin
Senior Compositor: Gloria Schurick
Manufacturing Buyer: Dan Uhrig

© 2012 by Pearson Education, Inc.
Publishing as FT Press
Upper Saddle River, New Jersey 07458

FT Press offers excellent discounts on this book when ordered in quantity for bulk purchases or special sales. For more information, please contact U.S. Corporate and Government Sales, 1-800-382-3419, corpsales@pearsontechgroup.com. For sales outside the U.S., please contact International Sales at international@pearson.com.

Company and product names mentioned herein are the trademarks or registered trademarks of their respective owners.

All rights reserved. No part of this book may be reproduced, in any form or by any means, without permission in writing from the publisher.

Printed in the United States of America

First Printing August 2011

Pearson Education LTD.
Pearson Education Australia PTY, Limited.
Pearson Education Singapore, Pte. Ltd.
Pearson Education Asia, Ltd.
Pearson Education Canada, Ltd.
Pearson Educación de Mexico, S.A. de C.V.
Pearson Education—Japan
Pearson Education Malaysia, Pte. Ltd.

Library of Congress Cataloging-in-Publication Data

Ito, Masao, 1928-
The cerebellum : brain for an implicit self / Masao Ito.
p. ; cm.

Includes bibliographical references.

ISBN-13: 978-0-13-705068-0 (hardback : alk. paper)
ISBN-10: 0-13-705068-2 (hardback : alk. paper)

1. Cerebellum—Physiology. 2. Neuroplasticity. I. Title.
[DNLM: 1. Cerebellum—physiology. 2. Motor Neurons—physiology. 3. Neuronal Plasticity. 4. Synaptic Transmission—physiology. WL 320]

QP379.I85 2012

612.8’27—dc22

2011010870

ISBN-10: 0-13-705068-2

ISBN-13: 978-0-13-705068-0

To my wife, Midori Ito

This page intentionally left blank

Contents

Preface

The primary rationale for my writing this book is that I have been involved in research on the cerebellum for half a century and it seemed appropriate to share with younger generations of researchers how thrilling and dramatic this epoch has been, particularly since research on the cerebellum has advanced not only our understanding of this fascinating structure but also that of overall neuroscience. I also have another rationale, however, which is more implicit but no less compelling. This is the desire to know how and to what extent we might proceed toward the goal of completely understanding the human brain, not only the detail of its huge mass of neurons, but also the means by which it can generate human intelligence, which has evolved over millions of years. Current systems neurobiology addresses this issue to some extent, but available methodology and technology are limited and guiding hypotheses are still sparse. To this end, research on the cerebellum is on the forefront for asking the question "How does our brain accomplish its most complex and sophisticated actions?

Forty-five years ago, I co-authored the monograph *The Cerebellum as a Neuronal Machine* with John Eccles and Janós Szentagothai. This book described several neuronal circuits of the cerebellum, using analytical techniques that had advanced greatly in the late 1950s and early 1960s. Seventeen years later, I wrote a monograph *The Cerebellum and Neural Control.* Its focus was on the role of long-term depression in the cerebellum and this structure's control of the vestibulo-ocular reflex. Such work suggested to me that the cerebellum was capable of learning and thereby played an essential role in adaptive neural control. In that 1984 book, the cerebellum was viewed as an assembly of many modular units (microcomplexes), each of which constituted a neurocomputing machine embedded in a control system of the brainstem and/or spinal cord. The book also contained a germ of the idea that the cerebellum performed internal model-based controls that were delineated and formulated computationally a few years later (in 1987) by Mitsuo Kawato and his colleagues.

This 2011 monograph discusses advances made since 1984 in the overall study of neuronal circuits and the adaptive and model-based control of movement. It also presents new developments concerning the involvement of the cerebellum in motor actions and cognitive functions. The subtitle of the book, "Brain for an Implicit Self," reflects my current view of the cerebellum. Its role in the adaptive control of movement is performed unconsciously. Even though voluntary movements, such as those needed to ski, skate, or play a piano, and so on, are performed under conscious awareness (of at least some components of the movements), there is no such awareness when these movements become more refined due to their practice. A similar situation prevails for our thoughts. When we think about some topic repeatedly, the thought becomes more and more implicit; that is, it requires less and less conscious effort, as in intuition. This suggests that the cerebellum aids the self in both movement and thought, but covertly, by use of its internal models. The question of just how neuronal circuits of the cerebellum can accomplish such an all-encompassing role will be a major challenge in the coming decades.

I wish to thank all the cerebellar researchers cited in this monograph, whether living or deceased. Their expertise embraced, or continues to embrace, both the traditional disciplines of anatomy, physiology, biochemistry, pharmacology, and pathology and the many newer subdisciplines of neuroscience that derive their merit from both the life and physical sciences. Over the years these disciplines have continued to generate both new experimental data and novel theories.

I am grateful to those who kindly permitted me to reproduce their illustrations in this monograph. I wish also to thank the many colleagues who spent some time in my laboratory at the University of Tokyo before 1989 and at the RIKEN Brain Science Institute after 1990. I am also greatly indebted to the University of Tokyo for strongly supporting my earlier research activity, particularly through the difficult period of campus disruption, and the RIKEN Brain Science Institute for providing me with such an excellent research environment.

In publishing this monograph, I am particularly thankful to Prof. Douglas G. Stuart, Regents' Professor Emeritus of Physiology, University of Arizona, for his advice about my use of the English language and discussions on posture and locomotion mechanisms. I am also indebted to Drs. Soichi Nagao and Tadashi Yamazaki, RIKEN Brain Science Institute, for our many discussions about the content of this monograph.

Finally, I wish fervently that research on the cerebellum in the coming decades will be fruitful, particularly in clarifying its neuronal mechanisms in processing information of both a motor and a cognitive nature. Such progress will be a major step in the unlocking of brain mechanisms that support the implicit self.

Acknowledgments

Grateful thanks are due to the publishers and editors of the following journals for their generosity in giving permission for reproduction of figures: Annual Review of Neuroscience (Annual Reviews), Journal of Neurophysiology (American Physiological Society), Journal of Neuroscience (Society for Neuroscience), Journal of Physiology London (The Physiological Society, John Wiley & Sons), Nature Reviews Neuroscience (Nature Publishing Group), Proceedings of National Academy of Sciences USA (National Academy of Sciences USA), and Progress in Brain Research (Elsevier). Grateful thanks also goes to the Instituto de Neurobiología "Ramón y Cajal," Madrid, Spain.

About the Author

Masao Ito is professor emeritus and former dean of the medical faculty at the University of Tokyo, and the founding director of the RIKEN Brain Science Institute. He has served as president of many international scientific organizations, including the International Brain Research Organization, the International Union of Physiological Sciences, the Human Frontier Science Program, the Science Council of Japan, and the Japan Neuroscience Society. Dr. Ito won the 1996 Japan Prize and the 2006 Gruber Prize in Neuroscience.

1

Neuronal Circuitry: The Key to Unlocking the Brain

1-1 Introduction

The central nervous system (CNS) of vertebrates contains an enormous number of neurons, each having elaborate electrical and chemical signaling mechanisms. These neurons are interconnected via synapses to form intricate neuronal circuits. While such a circuit is composed of molecules within cells, it also processes information and generates a multitude of functions. Much effort has been and continues to be devoted to bridging these two properties of neuronal circuits to explore still largely unknown mechanisms of the CNS. The circuits of the cerebellum have been on the forefront of this endeavor. This chapter addresses the methodologies and fundamental concepts that are currently being used in the study of generic complex neuronal circuits before focusing in succeeding chapters on the cerebellum.

1-2 Decomposition and Reconstruction

At a far earlier time, René Descartes (1596–1650) discussed the search for complex mechanisms of the universe and life by using the clock as a metaphor. During his time, this machine was considered the most complex of all the world's man-made structures. Following Descartes (1649), it can be argued, as is prevalent today, that if one can dismantle a clock into its pieces and then successfully reconstruct them into the same functional machine, the precise nature of the clock is revealed. This methodology is still widely applicable when examining an object of unknown nature. It is dissected into simpler pieces, which can be understood, and then an attempt is made to reconstruct a model composed of all the pieces. If this model exhibits all the properties of the original object, it is indeed understood.

The CNS includes the brain (contained within the skull), which weighs 1.3–1.4 kg in humans, and also the spinal cord, which extends into the vertebral canal. On the basis of conventional anatomy, the brain is grossly divided into the brainstem, cerebellum, and cerebrum. The cerebrum is further divided into the basal ganglia, limbic system, and neocortex (Figure 1). The cortex of the cerebral hemisphere is further subdivided to 52 areas (Brodmann, 1909; Garey, 1994) (Figure 2). The cerebellar cortex is also subdivided into nearly a hundred areas (see below and Color Plate II). Currently, we know that each of these divisions is composed of characteristic neuronal circuits that consist of numerous neurons of diverse types interconnected with each other via synapses. Moreover, there are even more numerous glial cells and finely branch blood vessels that support and nourish the neurons. The neuronal circuits in each subdivision constitute local networks, which are further integrated to form global neural systems across subdivisions or divisions. Current neuroscience is based on the belief that these networks and systems operate through specific mechanisms and play specific functional roles in the living body.

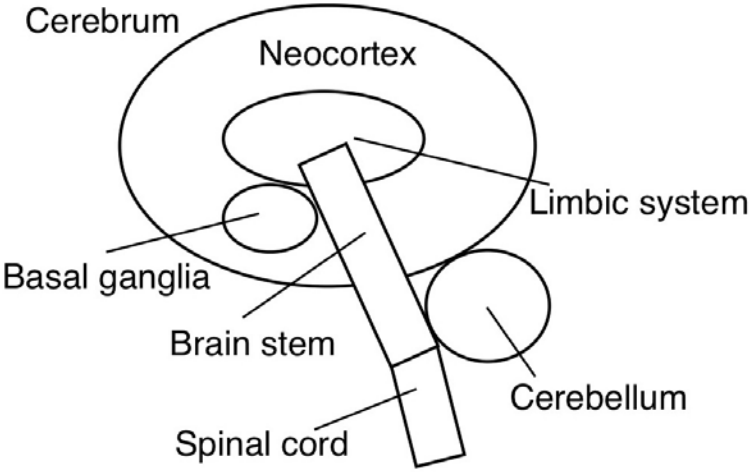

Figure 1 A sketch of major divisions of the CNS.

How can we unveil such mechanisms and the functional roles of neuronal circuits? The initial approach was to dissect the brain into experimentally manageable parts. This was the strategy adopted a century ago by Sherrington (1857–1952) and his group. They severed a segment of the cat spinal cord from its upper (and sometimes lower) segments (Figure 3A). Freed from the effects of other structures, the severed segments exhibited reflexes with stable, straightforward input-output relationships via the dorsal and ventral roots, which could be subjected to precise scientific investigation.

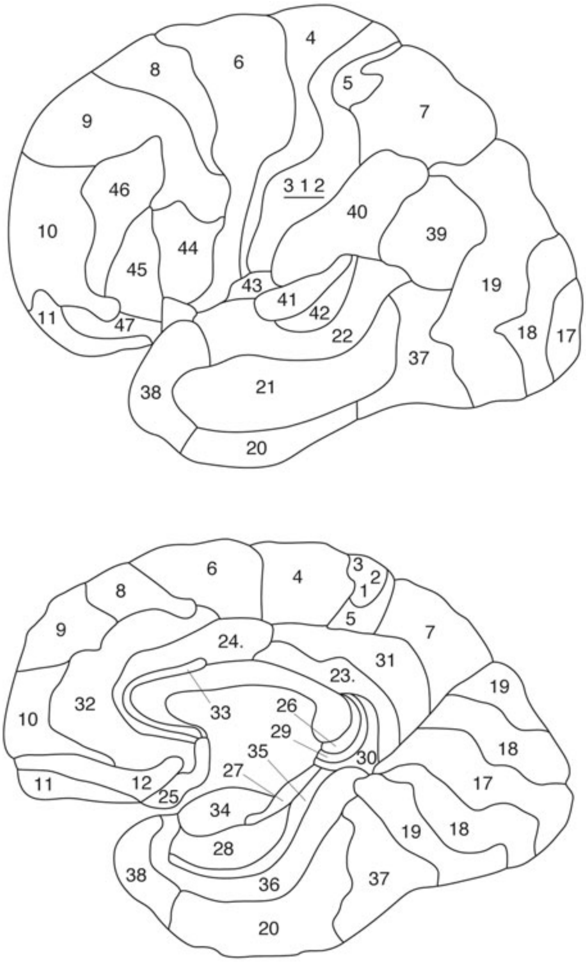

Figure 2 Brodmann's cerebral cortical areas.

The original dotted map published by Brodmann (1909) is converted here to outlined areas. (The original color version was provided by courtesy of Mark Dubin: http://spot.colorado.edu/~dubin/talks/brodmann/brodmann.html.)

When a neuronal circuit is defined in terms of its gross structure and function, it can then be decomposed into its individual neurons and their dendrites, axons, and synapses, using the currently available technologies of neuroscience. Thereafter, one may try to reconstruct a model of the initial reflex circuit by using the properties of all its constituent parts. In the process of reconstruction, the mechanistic principle(s) operating in the neuronal circuit may well be revealed.

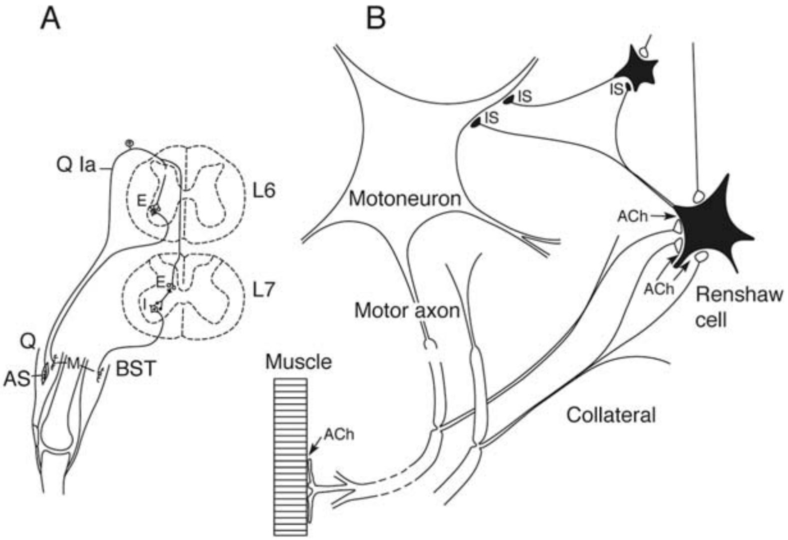

Figure 3 Sketch of some spinal reflex circuitry.

(A) Schematic of some spinal reflex pathways (modified from Eccles et al., 1954). (B) Spinal circuitry drawn by Eccles as based on his group's intracellular recording data on the recurrent Renshaw cell pathway (Eccles, 1963). In this and subsequent figures, sketches of a single cell and fiber (axon) usually represent groups of such units. A includes muscle spindles and their Ia afferents, two spinal cord segments, spinal motoneurons, Ia inhibitory interneurons, and two opposing muscles. B includes motoneurons and their axons supplying parts of muscle fibers, recurrent motor axon collaterals, Renshaw cells, and other spinal inhibitory interneurons. Abbreviations: ACh, acetylcholine; AS, annulospiral endings; BST, biceps and semitendinosus muscles; E, excitatory synapses: I/IS, inhibitory synapses; L6-L7, lumbar spinal segments; Q, quadriceps muscle; QIa, spindle Ia afferents supplying Q spindles. Symbols: black-filled neurons and their endings, inhibitory; open neurons and their endings, excitatory. This figure is dedicated to a 1963 Nobel Laureate, John Carew Eccles (1903–1997), who was my postdoctoral mentor in Canberra, Australia, from 1959 to 1962. (See Ito, 1997a, 2000; Stuart and Pierce, 2006.)

Sherrington's group assumed that peripheral stimuli induced excitatory and inhibitory "states" in the spinal centers for various reflex circuits. John Eccles (1903–1997) and his colleagues (e.g., Brock et al., 1952) later identified these as formed by the membrane depolarization and hyperpolarization of spinal motoneurons via excitatory and inhibitory synapses (Figure 3B). Hubel and Wiesel (1960) discovered the unique responsiveness of individual neurons to line stimuli in the visual cortex. They proposed a model of a neuronal circuit to explain how the characteristic responsiveness of "simple" and "complex" cells are formed, using input from concentric receptive fields of the lateral geniculate neurons. These early discoveries marked the start of modern neuroscience.

Neuroscience is now dominated by the effort to decompose neuronal circuits into their cellular and molecular components. Many would argue, however, that reconstructing models of such circuits is equally important in our attempt to comprehend their functional principles (e.g., van Hemmen and Sejnowski, 2006; Stuart, 2007; for biology as a whole, see Noble, 2006). In the reconstruction process, it is possible to uncover novel principles operating in the original neuronal circuits. Analogies to man-made systems such as computers, control devices, and communication networks have also been helpful, as emphasized in the field of cybernetics by Nobert Wiener (1894–1964).

The circular approach through decomposition and reconstruction provides a general method of fundamental research that features close interactions between experiments and theory (Figure 4). Initially, a factual observation of a complex subject may suggest a crude conceptual model, which serves to generate a prediction for a more focused experimental observation. If the prediction turns out to be correct, it supports the crude model, which is then refined to a more accurate conceptual model. This, in turn, can be converted into a substantial computational model, which is reproducible on a computer. Such an advanced model enables us to make further predictions, which can again be tested in even more precise experiments. In this iterative, cyclic development using observation-inspired models, model-based predictions, and experimental testing of the predictions, a model is continuously refined until it accurately simulates the complex subject.

A well-known and unique difficulty in research on the CNS arises from its highly hierarchical structure. Comprehension of our current understanding of the brain requires knowledge integrated across several hierarchical levels including molecules, cells, circuits, systems, and behaviors. It seems that ever since organic molecules appeared on earth, these hierarchical levels gradually accumulated through evolution until the human CNS evolved. The above-mentioned decomposition-reconstruction approach can be applied to any two successive levels of the overall hierarchy. For example, a simple neuronal circuit set can be reduced to its component neurons having somata, axons, dendrites, and synapses (Figure 5). In turn, these component neurons can be combined to reconstruct a model of the circuit at its original hierarchical level. Next, the component neurons can be further reduced to the lower level of ion channels, receptors, first and second messengers, and various organelles, whose combined properties can provide models of electrical and chemical signaling processes in neurons. Ion channels, receptors, and messenger molecules can be further reduced to an even lower level of proteins and their genes. The latter's properties can be incorporated into models of the original ion channels and signaling molecules. By this method, the initial simple neural circuit can be linked step by step (not by jumps) to the molecular mechanisms subserving neuronal functions.

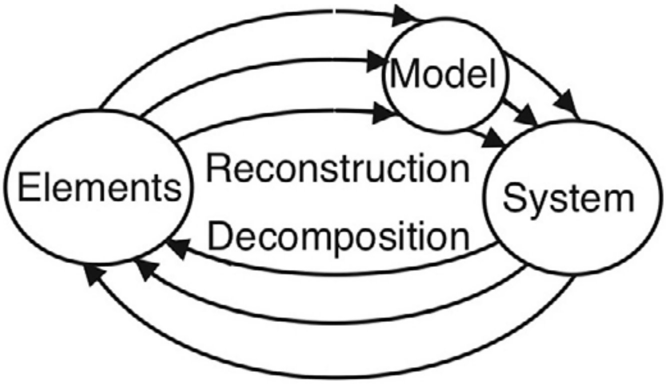

Figure 4 A decomposition/reconstruction cycle.

Research on the CNS starts usually with the experimental dissection of a relatively complex system into its simpler elements. To this end, a system is defined as a CNS unit (e.g., a spinal segment, the pineal body, oculomotor system) while it is undertaking a specific operation. In some cases the system can include peripheral effectors (i.e., glands, muscles). The dissected elements are assorted to construct models of the original system by means of theories and simulations. This circular approach may be based on observation-inspired models, model-based predictions, or experimental testing of a prediction. The model is continuously refined until it accurately simulates the complex system, as symbolized by three trajectories, which represent the first cycle (outer trajectory), an intermediate (middle) cycle, and the most refined (inner) cycle.

These processes can be considered as a long chain of decomposition-reconstruction events. By successively linking hierarchical levels, neuroscience research can trace the long pathway of evolution, from organic molecules to the cells of multicellular organisms, and eventually to the differentiated and diversified neurons that constitute simple neuronal circuits. In addition, evolutionary processes starting from simple neuronal circuits gradually led to the development of increasingly complex circuits and finally the human CNS. The fields of many subdisciplines of neuroscience are found at specific levels of the hierarchy. For one to understand the mechanisms and roles of neuronal circuits in the CNS, consistent and sustained effort is required to link coherently all levels of the hierarchy centering around neuronal circuits that extend to cells and molecules on one hand, and to complex networks and systems on the other. In later chapters, we will see how far the cerebellum has been decomposed and reconstructed using these general methodologies.

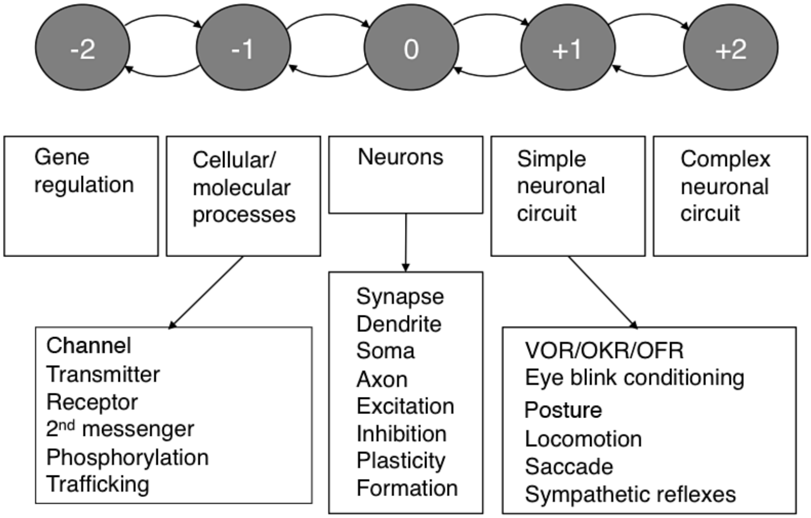

Figure 5 The progression of decomposition/reconstruction cycles.

Shown are levels of analysis that extend from gene regulation (-2) to the cellular/molecular- (-1), neuronal- (0), simple circuit- (+1), and finally, complex circuit (+2) level of analysis. Major themes at levels -1 to +1 are also shown.

1-3 Neurons and Synapses

The concept of the "neuron" was established over a century ago as the unitary component of neuronal circuits. Ramón y Cajal (1852–1934), hereafter shortened to "Cajal," presented clear evidence for this in 1888, when referring to the relationship between Purkinje and basket cells in the cerebellum (see below and Color Plate IV) (Lopez-Munoz et al., 2006). Heinrich von Waldeyer-Hartz (1836–1921) formally proposed the neuron theory in 1891. Also, near the end of the nineteenth century, Sherrington and Michael Foster (1836–1907) coined the term "synapse" and spotlighted it as a key structure of the CNS. Since then, neurons and synapses have been the major targets of neuroscience investigations. All neurons commonly have somata extruding axons and dendrites (except for dorsal root ganglion cells, which have no dendrites). Dendrites not only expand the membrane area to accommodate many hundreds of synapses, but they also have finely compartmentalized functions (Hausser and Mel, 2003). On the other hand, different types of neurons are distinguished by their characteristic morphology, spike activities, synaptic actions (excitatory or inhibitory), and synaptic receptiveness (chemical or electrical). Subcellular structures such as postsynaptic density (PSD), cytoskeleton, endoplasmic reticulum, Golgi organ, and mitochondrion support these neuronal functions. Signal transduction involves various transmitters, modulators, receptors (ionotropic or metabotropic, or both), and second messengers. For these molecular mechanisms of neurons, numerous proteins, glycoproteins, and lipids, and their genes play essential roles.

1-4 Neural Networks

Numerous neurons in the CNS assemble to form a structure called a "nucleus." In certain areas of the brain and spinal cord (e.g., the superior colliculus, cerebellar cortex, hippocampal cortex, cerebral neocortex), different types of neurons regularly assemble to form a multilayered network. Donald Hebb (1904–1985) proposed the concept of "neuron assembly," that is, a collation of neurons interconnected by synapses, in which the connectivity is modifiable according to experienced activities (Hebb, 1949). A famous proposal by Hebb is that the connection between two neurons firing synchronously is strengthened. Because of this "Hebbian" type of synaptic plasticity; a neuronal assembly can change its circuitry structure (corresponding to memory) and consequently modify its input-output relationships (corresponding to learning), as dependent on experienced activities.

In an effort to verify Hebb's concept of neuron assembly, Frank Rosenblatt (1928–1971) constructed a model network named a "simple perceptron." It consisted of three layers of neurons connected in one direction, from the sensory cell layer to the association cell layer, to the response cell layer (Figure 6). Connections from the first to the second layer were fixed, whereas those from the second to the third layer were modifiable according to the instruction of an outside "teacher." The teacher increased the weight of connection at all junctions transmitting signals from the second to the third layer when the simple perceptron responded correctly to sensory stimuli. The teacher decreased the weight at all second-to-third layer connections transmitting signals when the response was incorrect. When this training process was repeated, the simple perceptron improved its performance toward a success rate of 100%. This was the first man-made machine capable of learning. Ten years later, a counterpart of the simple perceptron was found in the cerebellum (see Chapters 3 and 9). The simple perceptron exemplified the success of the constructive approach (i.e., to understand by construction) for clarifying the operation of neuronal networks in the CNS.

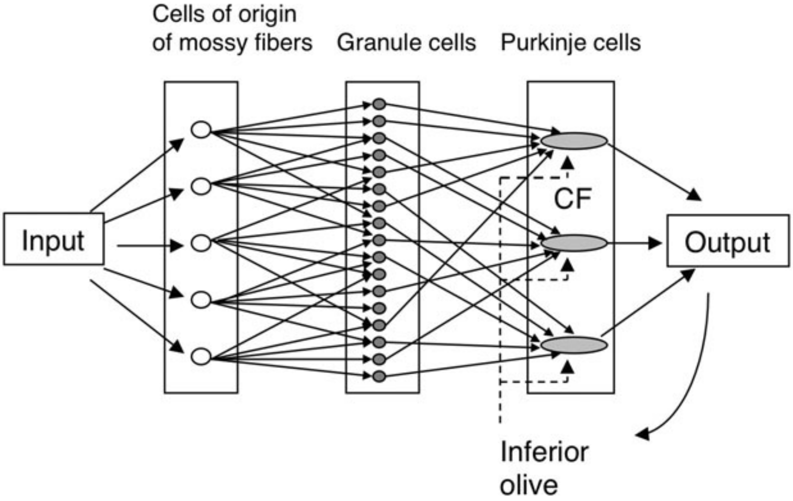

Figure 6 The simple perceptron model of the cerebellum.

This figure is self-explanatory. See the text for further details on the operation of a simple perceptron. Abbreviation: CF, climbing fiber.

Twenty-four years after the construction of the simple perceptron, another form of multilayered neuronal assembly was proposed. It is usually called a "neurocomputer" (Rumelhart et al., 1986), in which errors were estimated by comparing the output of the third layer with a preset goal and were back propagated to the third-layer neurons. The errors acted on the junctions on the third-layer neurons formed with second-layer (hidden layer) neurons, and modified the efficacy of transmission from second-layer to third-layer neurons. The neurocomputer is often applied to model information processing in hippocampal and neocortical networks.

1-5 Systems Control Mechanisms in the CNS

Local networks are interconnected globally throughout the CNS to form neural "systems." A major type of such a system has the general form of a "control system," which consists of a "controller (g)" acting on a "controlled object (G)" (Figure 7A). The controller receives input instruction that provides information about the nature of the required output (e.g., the goal, the trajectory of a movement). In turn, the controller generates command signals that drive the controlled object to respond appropriately. The controller may receive information about the performance of the controlled object (Figure 7A, feedback control), or it may operate without peripheral information (Figure 7B, feedforward control). The goal of a control system is to generate output responses identical to the input instruction. This can be achieved in a feedback control system if g is sufficiently larger than G, but in a feedforward control system, g needs to equal 1/G (Figure 7B). As emphasized by Baev (1999), this basic control system concept applies to various levels of organization within the CNS: in this monograph from reflexes to isolated voluntary movements and finally to coordinated motor actions. In addition, the concept is applied formalistically to cognitive functions.

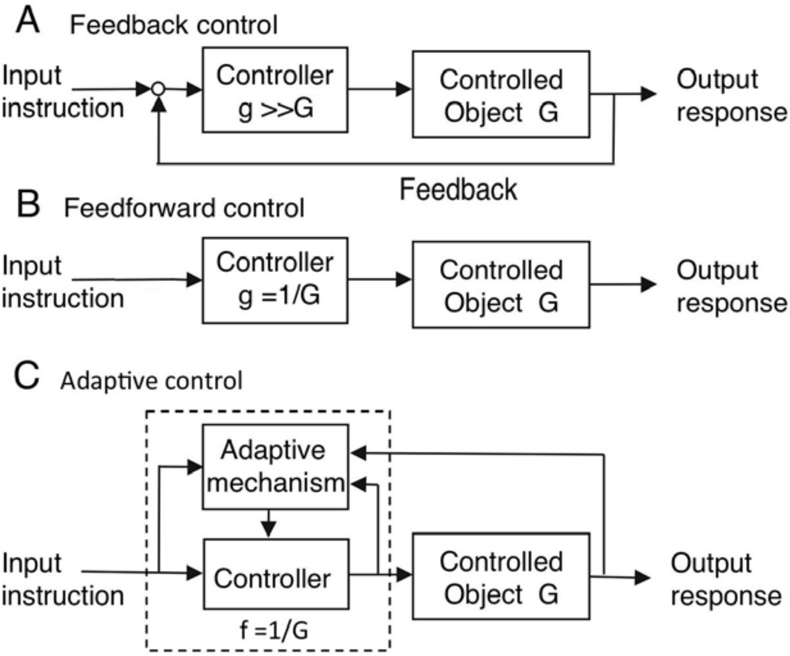

Figure 7 The fundamental structures of a control system.

(A) A basic feedback control system. (B) A basic feedforward control system. (C) An adaptive control system equipped with an adaptive mechanism. This schematic applies to the cerebellar control of reflexes.

In recent years, modern control theory studies have opened the new fields of "adaptive control" and "model-based control." In adaptive control, the controller is equipped with an adaptive mechanism to constitute an adaptive controller, which learns how to perform effectively in a given situation by altering its performance to match ever-changing environments. When a mechanism is attached to a feedforward controller, their overall input-output relationship f should be adjusted to 1/G (Figure 7C). On the other hand, model-based control was developed for robotic arm control (An et al., 1988), and it has opened a new field of computational neuroscience for research on the cerebellum (Kawato et al., 1987).

In the model-based control, a feedforward control system (Figure 7B) is attached with one of the two types of internal models, "forward" and "inverse" (Figure 8A, B). An internal forward model simulates the kinematics of a controlled object, whereas an internal inverse model simulates the dynamics or kinetics of them (for a definition, see Chapter 15, "Internal Models for Voluntary Motor Control"). Internal forward models support the controller by predicting the state of the system during actual actions. On the other hand, internal inverse models map the relationship between intended actions (or goals) and the motor command to bring about the action. An internal inverse model uses the desired position of the body as inputs to estimate the necessary motor commands, which would transform the current position into the desired one. An adaptive mechanism is involved to secure close simulation by these models. Such models may be formed in various parts of the CNS including, in particular, the elaborate neuronal networks of the cerebellar and cerebral cortices. Hereafter, models formed in the cerebellum and cerebral cortex will be called "cerebellar internal models" and "cerebral cortical models," respectively.

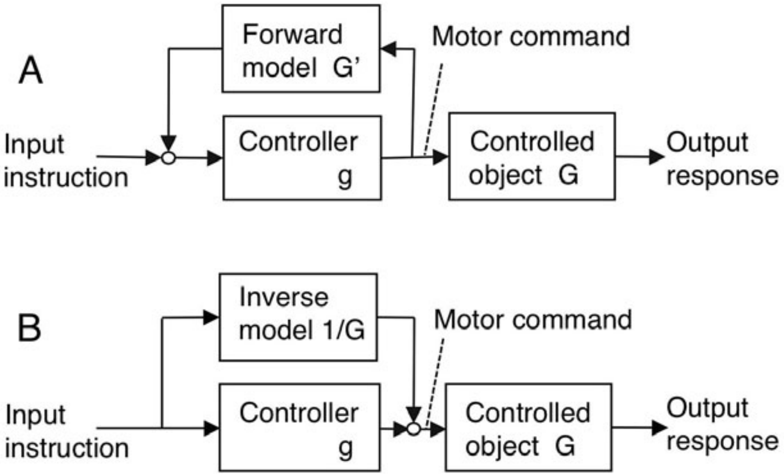

Figure 8 General forms of model-based control systems.

(A) Internal forward model (G') simulates the input-output relationship of the controlled object (G) and is inserted between the output and input of the controller (g). (B) Internal inverse model (1/G) simulates the output-input relationship of the controlled object (G) and is inserted between the input instruction and output response of the controller (g).

1-6 Reflexes and Voluntary Movements

The most fundamental control system structure in the CNS is an individual reflex operating via the spinal cord or brainstem. A reflex is performed by sequential activities in a neuronal circuit that connects serially sensory receptor cells, an afferent path, a reflex center, an efferent path, and an effector (a muscle, set of muscles, or a secretory gland or glands). This is typically exemplified by the stretch reflex, in which motoneurons maintain the length of a muscle constant by using feedback from muscle spindles (Chapter 11, "Somatic and Autonomic Reflexes"). In this case, a group of motoneurons and associated segmental interneurons constitute a controller, whereas the motor apparatus composed of the muscle(s) and a joint provides the controlled object. Numerous reflexes of various types operate in the spinal cord and brainstem to control simple somatic and visceral functions of a living body. The operation of reflexes is usually automatic—that is, it does not reach the level of conscious awareness—but in ever-changing environments it is indeed modifiable by use of adaptive mechanisms of the cerebellum (Chapters 10–12).

We traditionally consider voluntary movements as a much higher order of movements than reflexes in the sense that they are controlled by "free will" and can be performed both automatically and at the level of conscious awareness, whereas reflexes are driven by peripheral stimuli and executed solely by automatic means. However, as our understanding advances for neuronal mechanisms underlying voluntary movements, distinctions between such movements and reflexes become blurred because many of the same neuronal circuits are employed for both types of movement (Prochazka et al., 2000; Hultborn, 2001). Practically speaking, however, we may still distinguish voluntary movements as initiated from the cerebral cortex, whereas reflexes operate largely within the spinal cord and brainstem. Typically, two cortical areas, the primary motor cortex and the frontal eye field, are involved in voluntary movements of the limbs and eyes, respectively (Chapters 13 and 14). In the systems control parlance emphasized in this volume, reflexes and voluntary movements may share neuronal circuits for their controller and controlled object structures, but they are separated from each other by the nature of the instruction signals that drive the controller. Instructions for reflexes arise from periphery, whereas voluntary movements are driven by "top down" instruction signals generated in higher centers of the cerebral cortex, including but not limited to the supplementary motor cortex and the anterior cingulate gyrus (see Chapter 13, "Voluntary Motor Control").

An interesting idea has been put forward to suggest that a central instruction causes a voluntary movement by an imitation or replacement of the peripheral stimulus that induces a reflex (the imitation hypothesis; Berkinblit et al., 1986). For instance, the CNS can voluntarily elicit a saccadic eye movement by means of the imitation of the visual signals that could elicit the saccadic movement reflexively. In this sense, the central instruction may imply an "afference copy" of the peripheral stimulus. Such a capability of imitating a peripheral stimulus might emerge during evolution to develop a neuronal mechanism of voluntary motor control. Neuronal mehanisms underlying the postulated capability of imitation are unknown, but one may suppose that a group of neurons memorize those signals of peripheral stimuli that evoke a motor behavior reflexively and reproduce the same signals whenever a similar motor behavior is to be generated voluntarily. Here, one may recall the "mirror" neurons, which are present in certain cerebral cortical areas and are activated during both observed and performed hand actions, as discussed below (Section 8 and also in Chapter 16, "Motor Actions and Tool Use," Section 5). These neurons appear to memorize perceptive signals representing certain successful motor actions performed by another individual and reproduce them as central instructions for their own body's motor actions. Admittedly, however, the neuronal sites and mechanisms underlying free will in the high cerebral centers are still an enigma (Wegner, 2002).

1-7 Integration of reflexes

One of the major ideas that Sherrington outlined in his 1906 book "The Integrative Action of the Nervous System" was that complex actions of the nervous system could be composed of a collation of reflexes, somewhat like building a house by piling up bricks. From the control systems perspective, there now appear to be at least eight ways to integrate reflexes into the overall control of movement. First, many that are driven by different sensory inputs may share the same controller and controlled object (Figure 9A). For example, three types of relatively slow ocular reflexes are driven individually by vestibular or visual stimuli, as will be seen later in Chapter 10, "Ocular Reflexes." Nonetheless, they commonly share vestibular nuclear neurons as the controller, and eyeballs and the associated oculomotor system, as the controlled object. By this means, such a group of reflexes can achieve the common purpose of securing visual stability and acuity under natural behavioral conditions. In other words, these individual ocular reflexes are combined together to form a "multi-input" control system. Second, several individual reflexes may have different controllers (Figure 9B, Reflex 1, 2, 3 controllers), but they may share the same controlled object. For example, a slow ocular reflex can be integrated with a brisk saccade only in the form of half-fused control because these eye movements require controllers having substantially different properties for generating slow and brisk eye movements, respectively (Chapter 10). Third, reflexes may also be combined with a voluntary motor control system in a hybrid way (Figure

9C) because of the similarity of control system structures for reflexes and voluntary movements (see Section 6). Design problems in such hybrid systems will be discussed later (Chapter 15).

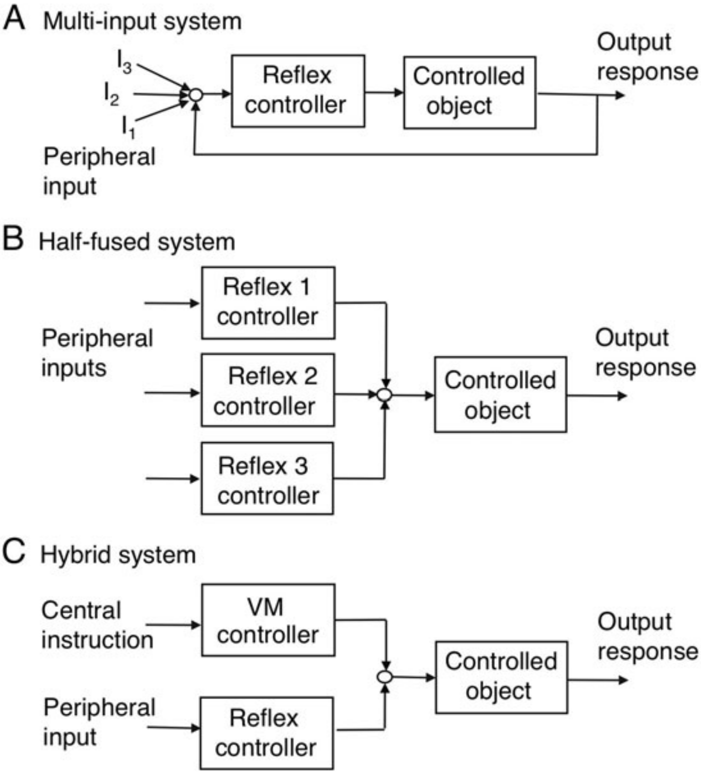

Figure 9 Schematics of types of integrated reflex control.

(A) A multi-input reflex. (B) Half-fused system. (C) Hybrid control of a reflex and a voluntary movement. For further explanation, see the text. Abbreviations: $I_{1,2,3}$, three sensory inputs of different modality; VM, voluntary movement.

The spinal cord and brainstem contain a collation of reflexes to elaborate compound movements such as when assuming a posture, or when walking, swimming, and flying. Hence, a fourth way of integration is for some reflexes to be combined by mutual interaction (Figure 10A, Reflexes 1 and 2). For example, when one explores the visible world, a saccade and a head movement, the latter inducing the vestibuoocular reflex, occur in combination. This eye-head coordination involves an inhibitory cross talk between the independent eye and head controllers (Kardamakis and Moschovakis, 2009). A fifth way is for reflexes to be compounded when signals in a descending tract activate some combinations of reflexes to express behaviorally meaningful compound reflexes (Figure 10B, for review, see

Lemon, 2008). Anders Lundberg (1920–2009) and his colleagues found a good example in the cervical segments of the spinal cord. In the C3–C4 propriospinal system of the cat, interneurons were shown to receive extensive convergence from different primary sensory afferents and supraspinal centers (Lundberg, 1999; Alsternark et al., 2007). Through excitation or inhibition of relevant interneurons in this system, signals of each descending tract could produce compound reflexes to provide desired movement patterns, such as target reaching by the hand (Chapter 13). Operation of segmental spinal circuits sometimes involves a type of function generator (FG in Figure 10B, b). Locomotion is a good example of this type of compounding reflex. It involves flexion reflexes, crossed extension reflexes, interlimb coordination, and, in addition, a central pattern generator (CPG) mechanism for rhythm generation (Grillner et al., 1991, 2007; Grillner and Jessel, 2009) (see Chapter 11).

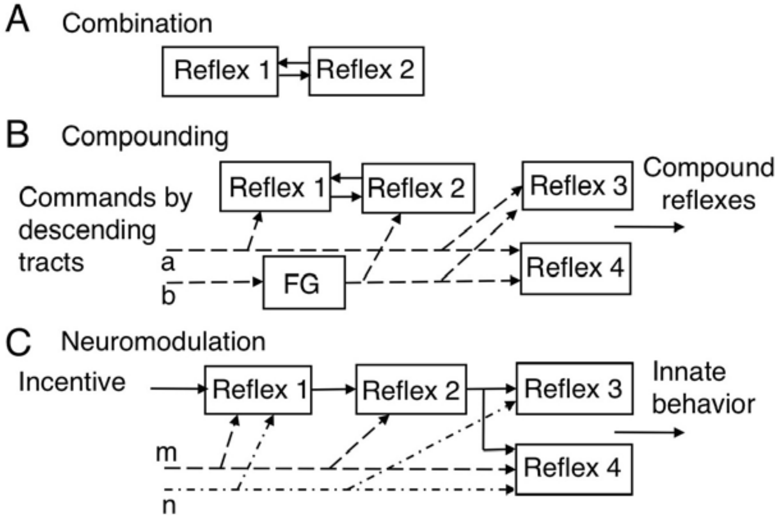

Figure 10 Schematics of the mutual interaction, compounding, and neuromodulation of reflexes.

Arrows denote synaptic actions, either excitatory or inhibitory. A shows how reflexes are combined by mutual interactions (Reflexes 1 and 2). In B, the compounding of reflexes 1, 3, and 4 is brought about by commands from descending tracts (a). Alternatively, reflexes 2, 3, and 4 can be coactivated by descending tracts (b) via FG, a function-generator. C shows how reflexes are modulated by aminergic and/or peptidergic innervation (represented by m and n) to exhibit a specific pattern of combination for behavior (m to reflexes 1, 2, and 4 and n to reflexes 1, 3, and 4). "Incentive" means a stimulus that leads to a specific behavior.

The sixth way to integrate reflexes is by "neuromodulation." As demonstrated in the crustacean stomatogastric nervous system (Marder et al., 1986; Selverston 1995), a small amount of a single peptide or amine may instantaneously rewire a neuronal circuit and switch behavior expression of the system. This mechanism may apply to the hypothalamus located in the most rostral and ventral part of the brainstem, which regulates innate behaviors including food intake, drinking, and reproduction; they are evoked by incentives such as the need for food, water, and reproductive activity, respectively. These behaviors involve a series of complex movements in order to approach and acquire the incentives. On the other hand, noxious stimuli such as drinking stale water or the figure of an enemy induce aversion, aggression, or defense reactions. An innate behavior involves a combination of reflexes and compound movements. For example, food intake involves locomotion to approach the food, rhythmic mastication, and the swallowing reflex. The hypothalamus contains a number of innate behavioral centers, each of which produces a specific pattern of behavior by secreting a neuromodulator substance through their widely distributed axons in the brainstem and spinal cord. The secreted neuromodulator substance may activate or inhibit a number of component reflexes and compounded movements (Figure 10C); hence, one circuit can be configured to perform a variety of different behaviors by activating neurons via certain types of neuromodulator receptors.

The seventh way to use reflexes, and probably the most important in regard to the cerebellum, is by "nesting" (as in "matryoshka"), which has been used to explain perceptual organization (Leyton, 1987) and even the entire hierarchical organization of the CNS (Baev, 1999). The nesting idea is that a reflex composed of a controller and controlled object at the lowest level can be regarded as a controlled object at the next higher level. For example, a stretch reflex is a control system at the segmental level (Figure 11A), but at a brainstem level, it acts as the controlled object of the vestibulospinal descending tract neurons, which act as the controller (Figure 11B). In a similar vein, the primary motor cortex acts as a controller of the spinal segmental circuits, which are the controlled objects (Figure 12A, B). Furthermore, the entire corticospinal system constitutes a controlled object for the premotor cortex, which serves as its controller (Figure 12C). Through use of this nesting principle, collective reflexes integrated in the previous six ways constitute a controlled object for a higher-level controller, which can thereby exert control over many reflexes in various combinations.

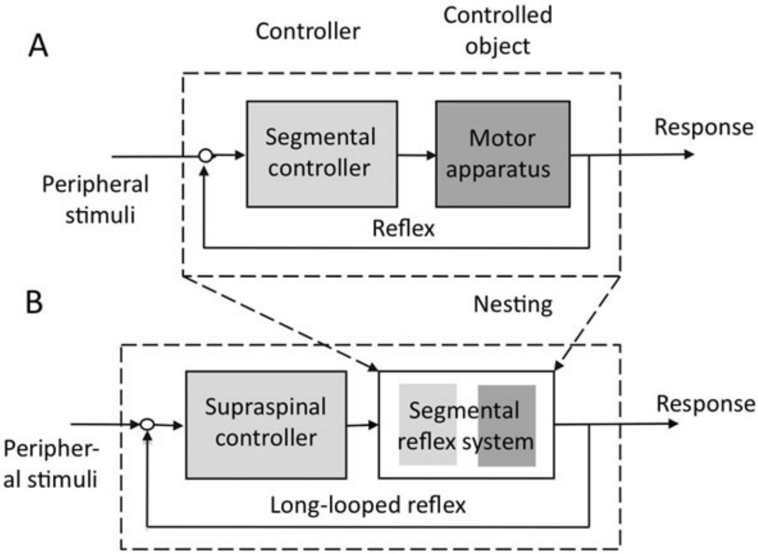

Figure 11 The one-step nesting of a reflex within a supraspinal controller.

(A) The control system structure of a segmental reflex. (B) A being nested within the controlled object of a supraspinal controller. For further details, see the text.

Finally, the imitation hypothesis discussed in Section 6 provides the eighth strategy used by the CNS to evolve voluntary motor control systems utilizing the reflex control systems formed in the brain stem and spinal cord as a basement structure.

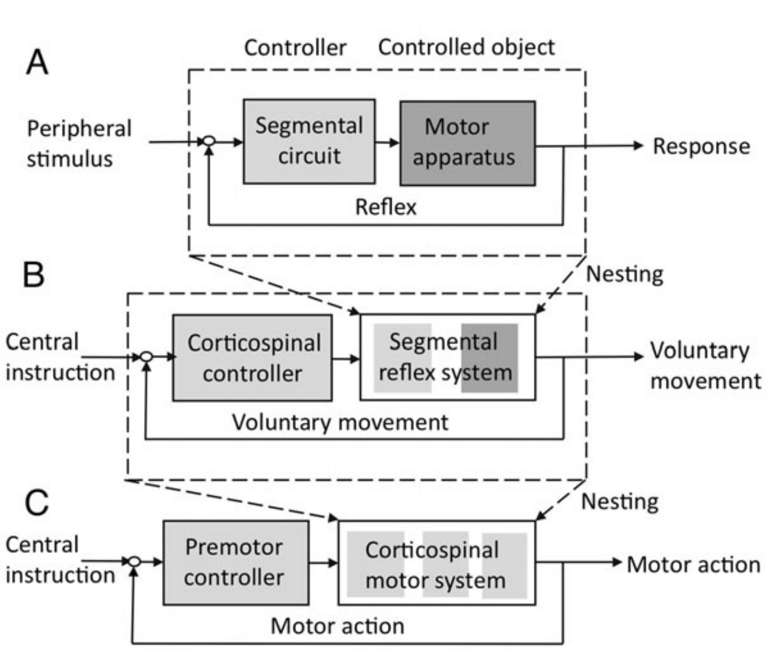

Figure 12 The two-step nesting of a reflex within the premotor cortical control of a motor action.

(A) and (B) are similar to those in Figure 11. (C) shows a further nesting for control at a cortical level.

1-8 Motor Actions

In the study of voluntary movements, the convention is to begin with analysis of a simple movement such as flexion of an elbow. However, voluntary movements that we perform daily are parts of "motor actions" that involve the participation of many body parts and even use of a tool to attain a purposeful goal. Moreover, motor actions also involve perceptual and conceptual activities, for example, in piano playing and dancing. It has been suggested that an "action schema" representing and coding motor actions is expressed in the posterior parietal and premotor (Brodmann's area 6, see Figure 2) cortices (Jeannerod, 1994). For the present purposes, an action schema can be considered to be a cerebral cortical model.

In primates, the premotor cortex expands rostrally from the primary motor cortex. It is generally assumed that the premotor cortex, in particular its dorsal part, plays a major role in computing and controlling complex motor actions (Wise et al., 1997). Moreover, the premotor cortex includes "mirror neurons," which discharge similarly during a motor action performed by the self or by another

2004). Based on these and other lines of evidence presented in Chapter 16, we assume that the premotor cortex acts as the controller of motor actions. The premotor controllers act on controlled objects, which nest the primary motor cortex and lower motor systems (see Figure 12C). The postulated action schema is assumed to reside in the temporoparietal cortex and provide a cerebral cortical model to the premotor cortex. The same control system structure may apply to tool use if a tool is represented in an action schema together with body parts (Chapter 15).

Action schema may include two related concepts (actually CNS properties) that are prominent in psychology: the "body schema," which possesses a continually updating map of the self's body shape and postures; and the "motor schema," the self's long-term memory structure capable of being retrieved as a whole, and then controlling the elaboration of motor skills composed of complex actions and movements. Both schemata are acquired or at least further refined by learning (Arbib, 2005; Stamenov, 2005). Along with the model-based control concepts discussed above (Section 5), these body/motor schemata can be considered as components of cerebral cortical models representing the forward and inverse models of the controlled object (Figure 8). These cerebral cortical models are presumably acquired during the initial learning of motor actions. As learning advances, the acquired body schema and motor schemata are transferred to cerebellar internal models (Chapter 15).

1-9 Thought as a Control Mechanism

The various forms of control systems discussed above operate in the physical domain. Our CNS moves various body parts daily by contracting or relaxing muscles to make a purposeful movement. Analogously, we manipulate daily a thought in the mental domain. For example, we use languages, make evaluations, and come to decisions, these being major components of human intelligence. Formalistically, as a controlled object, an idea or concept in the mental domain is analogous to a body limb in the physical domain. At present, however, there is as yet no experimental or computational way to bridge the physical and mental domains that operate in the CNS. Hence, any postulated thought control mechanism has no unequivocal representation in neuroscience.

Nevertheless, we find some concepts in the field of psychology that mediate physical and mental domains. For example, there is the term "mental model," which Craik (1943) and Johnson-Laird (1983) defined as a psychological substrate for a mental representation of real or imaginary situations. It is defined as a small-scale model of reality that the mind constructs and uses to reason, underlie explanations, and anticipate a future event. More concretely, mental models in psychology are representations of images, concepts, and ideas. One may also recall another term in psychology called "schema," which Jean Piaget (1896–1980) defined as being formed in a growing child learning to interpret and understand the surrounding world (Piaget, 1951). Piaget's schema includes both a category of knowledge and the process of obtaining that knowledge.

Currently, the above two concepts are not mechanistic, and they lack a computational basis. Hence, the examples presented below in Chapter 17, "Cognitive Functions," are largely hypothetical. Nevertheless, I believe that once neural correlates of a mental model and Piaget's schema have been established, the present well-accepted control system models that exist in the physical domain will be shown to also apply to the mental domain, and thereby help understand various cognitive mechanisms.

1-10 Beyond Movements

Figure 8, which shows model-based control system designs, may be referred to for considering a mental model as a controlled object. For the present, computer simulation cannot reproduce this model because it lacks a computational basis. This difficulty is like the one that arose in the field of artificial intelligence. More than 50 years ago, a group of computer scientists proposed a study that would "... proceed on the basis of the conjecture that every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it." These scientists were eager to make "... an attempt to find how to make computers that use language, form abstractions and concepts, solve kinds of problems now reserved for humans, and improve themselves" (McCarthy et al., 1955). This tempting approach in artificial intelligence, however, remains unsuccessful because it lacks the clarification provided by neural network mechanisms that can encode a concept or a specific piece of knowledge.

Another profound question is how the operation of a neuronal circuit can be undertaken with conscious awareness. Sigmund Freud (1856–1939) and many more recent researchers have emphasized that only a few of the activities of the CNS are executed consciously. For example, one cannot bring to conscious awareness the thought processes involved in improving motor skills (e.g., skiing) by training (non-declarative memory). In contrast, one can readily recall cognitive experiences (declarative memory) (Squire, 2009). In other words, the neuronal circuits implicated in non-declarative memory are remote from the mechanisms of conscious awareness, whereas those involved in declarative memory are closely connected to conscious awareness. On the other hand, it has been shown that

1976; Koch et al., 2006) and basal ganglia (Chen et al., 2006) has no impact on conscious awareness. Conventionally, intelligence has been considered to require consciously activated cortical functions, but a substantial part of it is probably exerted subcortically and consequently unconsciously. In fact, intuitive thought is an important part of intelligence, but it is exerted unconsciously without obvious reasoning (Chapter 17).

Neuroscience has reached a level of sophistication that is on the verge of addressing neural mechanisms underlying intelligence and conscious awareness. It seems likely that research on the cerebellum will be on the forefront of this endeavor.

1-11 Scope of This Monograph

In the chapters that follow, the neuronal circuits of the cerebellum are decomposed and reconstructed as explained in this chapter. Early and recent historical material is presented in Chapters 2 and 3, and Chapters 4–9 update understanding of the cerebellum as an elaborate neuronal and molecular machine. Next, recent progress is presented about how this machine provides an advanced type of systems control for reflexes (Chapters 10–12) and voluntary movements (Chapters 13–15). The material covered in Chapters 10–15 reviews findings that came mainly after my 1984 book, *The Cerebellum and Neural Control*, and Barlow's 2002 monograph, *The Cerebellum and Adaptive Control*. Chapters 16 and 17 examine the new possibility that the involvement of the cerebellum goes beyond movements to the higher-level functions of motor actions and cognition. The last Chapter 18, "Concluding Thoughts," includes a summary of points made in preceding chapters about structural-functional relationships in neuronal circuit structures of the cerebellum as developed step by step in evolution.

1-12 Summary

The decomposition-reconstruction method provides a logical and effective approach to studying the structure-function relationships of neuronal circuits. They are composed of local multilayered networks that interconnect globally to form neural control systems. Reflexes are the most fundamental units of neuronal circuits. Multi-input, half-fused, hybridized, mutually interacting, compounding, neuromodulating, nesting, and imitating are the eight ways to integrate reflexes into complex movements, voluntary movements, and innate behavior. A further integrated control is needed for both motor actions and, as yet to be determined, the mechanisms of cognitive thought.

Index

FT Press
FINANCIAL TIMES

In an increasingly competitive world, it is quality of thinking that gives an edge—an idea that opens new doors, a technique that solves a problem, or an insight that simply helps make sense of it all.

We work with leading authors in the various arenas of business and finance to bring cutting-edge thinking and best-learning practices to a global market.

It is our goal to create world-class print publications and electronic products that give readers knowledge and understanding that can then be applied, whether studying or at work.

To find out more about our business products, you can visit us at www.ftpress.com.