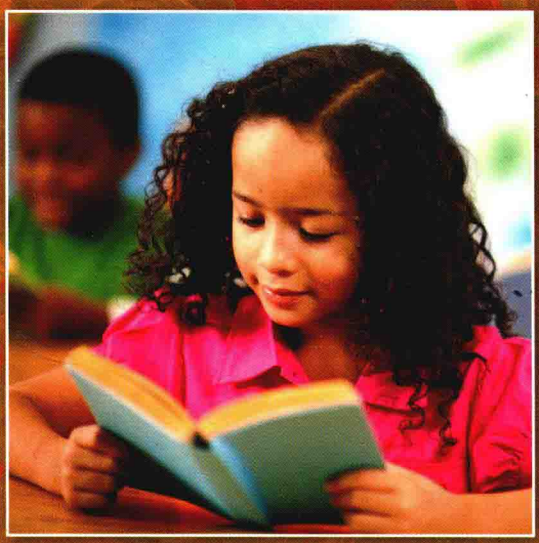
The Cerebellum

Learning Movement, Language, and Social Skills

Dianne M. Broussard



WILEY Blackwell

The Cerebellum

Learning Movement, Language, and Social Skills

Dianne M. Broussard

常州大学图书馆
藏书章

WILEY Blackwell

This edition first published 2014 © 2014 by John Wiley & Sons, Inc.

Editorial offices: 1606 Golden Aspen Drive, Suites 103 and 104, Ames, Iowa 50010, USA
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
9600 Garsington Road, Oxford, OX4 2DQ, UK

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell.

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Blackwell Publishing, provided that the base fee is paid directly to the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923. For those organizations that have been granted a photocopy license by CCC, a separate system of payments has been arranged. The fee codes for users of the Transactional Reporting Service are ISBN-13: 978-1-1181-2563-2/2014.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book.

The contents of this work are intended to further general scientific research, understanding, and discussion only and are not intended and should not be relied upon as recommending or promoting a specific method, diagnosis, or treatment by health science practitioners for any particular patient. The publisher and the author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of medicines, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each medicine, equipment, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. Readers should consult with a specialist where appropriate. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

Library of Congress Cataloging-in-Publication Data

Broussard, Dianne M., author.
The cerebellum : learning movement, language, and social skills / Dianne M. Broussard.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-118-12563-2 (cloth : alk. paper) – ISBN 978-1-118-73007-2 (emobi) –
ISBN 978-1-118-73013-3 – ISBN 978-1-118-73025-6 (epdf) – ISBN 978-1-118-73034-8 (epub)
I. Title.
[DNLM: 1. Cerebellum. 2. Executive Function. 3. Neural Pathways–physiology.
4. Psychomotor Performance–physiology. WL 320]
QP379
612.8′27–dc23

2013027959

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Cover images: Background art: Margaret Belknap; Top right: Dianne M. Broussard; Bottom left: © istock photo: CEFutcher; Bottom right: © istock photo: PicturePartners
Cover design by Modern Alchemy LLC

Set in 9.5/12.5pt Palatino by Aptara® Inc., New Delhi, India
Printed and bound in Singapore by Markono Print Media Pte Ltd

1 2014

The Cerebellum

Learning Movement, Language, and Social Skills

Acknowledgments

I would like to thank my teachers for having such different views about the same part of the brain. Maurizio Mirolli introduced me to the cerebellum. Hiroharu Noda, Bob McCrea, and Steve Lisberger made it clear that the cerebellum is a worthwhile and fascinating problem. I would also like to thank Helen Bronte-Stewart for her beautifully clear explanation of Marr's hypothesis, long before I found the time to actually read his paper; and Tom Masino, for asking me, "So what does the cerebellum do, anyway?" It took a bit of time, but here is my answer.

All of my colleagues and students have inspired me to write this book; it is really for them, and for their students. I thank Chris de Zeeuw, Jennifer Raymond, Kathy Cullen, Jim Sharpe, Dave Tomlinson, Doug Tweed, Sascha du Lac, Dora Angelaki, Albert Fuchs, Rich Krauzlis, Fred Miles, Jim McElligott, and many others, for asking good questions. I especially thank Jerry Simpson, for being skeptical about the cognitive function of the cerebellum.

My husband and colleague, David R. Hampson, first made me aware of the need for this book by getting me involved in his research on autism spectrum disorders. He has helped in innumerable ways. Thank you especially for the many hours of reading, the feedback, and the many discussions.

Finally, I am tremendously grateful to my daughter, Luci Belknap, for her constant support, encouragement, and sympathy through the long process of writing, and for the cover art.

此为试读,需要完整PDF请访问: www.ertongbook.com

Introduction

Early modern humans had a problem with brain size. These Stone Age humans probably had very high maternal and infant mortality, even higher than in the so-called primitive societies of modern humans, thanks to their larger crania. The expansion of the cerebral hemispheres had also made it necessary for babies to be born at a more immature stage than modern humans are. What if an increase in the size of the cerebellum, which was relatively small in Cro-Magnon Man, could improve the efficiency of the human brain, allowing the cerebral hemispheres and the diameter of the cranium to become slightly smaller, while maintaining the competitive edge provided by human intelligence? Although we do not know if this in fact did happen, it is consistent with what we do know (Weaver 2005). Such an improvement could have allowed more infants, and mothers, to survive childbirth while also allowing infants to be more mature at birth.

The cortex of the cerebellum is a huge, multilayered sheet of neurons that is folded like an accordion. The folds are compressed into a structure resembling a "little brain," which lies behind and beneath the cerebral hemispheres. But it is not really so little. In humans, if all of its folds were flattened out, the cerebellar cortex would extend for more than 1 m from front to back (Braitenberg & Atwood 1958). Several million nerve fibers exit the cerebellum (Glickstein *et al.* 2011). What is the function of all of this processing power and connectivity? What does the cerebellum do? In this book, I will argue that the cerebellum is a supplementary processing device that boosts the computing power of the cerebral cortex—and that it can be used for essentially any task.

It has been said that people born without a cerebellum are nearly normal, but this is a myth. In fact, the few patients with "cerebellar agenesis" have symptoms resembling severe cerebral palsy. In all known cases, their deficits include severe motor disability and profound mental retardation. What is more, the cerebellum is not completely lacking in any of them; some part of it always remains (Glickstein 1994). In fact, the number of cases where the cerebellum has been confirmed to be completely lacking in an individual who survived infancy is zero.

Individuals can survive without most of their cerebellum, but they need a lot of help. Also, we can walk and talk without parts of the cerebellum, just not very well. The cerebral cortex is plastic, and can learn without the cerebellum, and even (to some extent) can compensate for its absence. But having a cerebellum allows us to speed up, perfect, and extend our

behavioral repertoire. For animals in the wild (and even occasionally for modern humans), speed is absolutely crucial for survival. Good motor performance can be a matter of life and death.

The first goal of this book is to give a general overview of cerebellar function: what it does, and how it does it. Section I will focus on how the cerebellum works. Section II will show how the cerebellum participates in motor learning. Section III will describe the contribution of the cerebellum to precision, timing, and coordination of movement. Motor control is one of the most complicated things that animals—including humans—do, and the motor functions of the cerebellum allow us to interact promptly and successfully with our environment.

But the cerebellum also has other functions that have nothing to do with motor control. As we will see in Section IV, these include certain aspects of cognition: language, working memory, and attention as well as certain emotional and social functions. More cerebellar functions almost certainly remain to be discovered. There have been difficulties obtaining evidence for nonmotor cerebellar functions, mostly because we are talking about faculties that are exclusively human. The quality of the evidence is improving rapidly, but many clinicians and neuroscientists still believe that "the cerebellum is for motor control." My second goal is to demonstrate that this view should be changed.

REFERENCES

Braitenberg, V. & Atwood, R.P. (1958) Morphological observations on the cerebellar cortex. *J. Comp. Neurol.*, **109**, 1–33.

Glickstein, M. (1994) Cerebellar agenesis. *Brain*, **117**, 1209–1212.

Glickstein, M., Sultan, F. & Voogd, J. (2011) Functional localization in the cerebellum. *Cortex*, **47**, 59–80.

Weaver, S.H. (2005) Reciprocal evolution of the cerebellum and neocortex in fossil humans. *Proc. Natl. Acad. Sci. USA*, **102**, 3576–3580.

Contents

Acknowledgments ix
Introduction xi

Section I: The Neuronal Machine 1

1 Structure and Physiology 3
Anatomy of the Cerebellar Cortex 3
Physiology of the Cerebellar Cortex 6
Subdivisions of the Cerebellum 10
The Gatekeepers: Vestibular and Deep Cerebellar Nuclei 13
Afferent Connections of the Cerebellum 15
Efferent Connections of the Cerebellum 19
References 21
Further Reading 25

2 Operating the Machine 27
Learning in the Cerebellar Cortex 28
Pattern Recognition by the Cerebellum 30
Neural Networks 32
The Cerebellum as Part of a "Control System" 32
Multiple Sites for Cerebellar Learning? 34
The Cerebellar Clock 36
Conclusions 38
References 38
Further Reading 40

3 Plasticity in the Cerebellar Cortex 41
Cerebellar Long-Term Depression 41
The Calcium Trigger 42
The Synaptic Conversation 44
The Memory Trace 46
What About Potentiation? 48
Other Sites of Plasticity 51
Interneurons 52
Conclusions 55
References 55
Further Reading 59

4 Adjusting the Memory Trace 61
Consolidation Mechanisms 61
Memory Transfer and Synaptic Plasticity 63
Mossy-Fiber Collaterals in the DCN 64
Intrinsic Plasticity in the DCN 66
Other Changes to the Memory Trace 67
References 68

Section II: Motor Learning 71

5 Learning a New Motor Response 73
Learning in the Cerebellar Cortex 75
Cerebellar LTD and Learning 76
The Engram for the NMR 79
Conclusions 82
References 82
Further Reading 85

6 Recalibration for Fine Motor Control 87
A Stable Platform for Vision 87
Adjusting an Orienting Movement 95
Adjusting a Tracking Movement 97
Conclusions 99
References 99
Further Reading 102

7 Perfecting Limb Movements by Motor Learning 103
Updating Dynamic Models 104
Throwing and Pointing 107
Sequence Learning 109
Stepping and Changes to gait 111
The Agile Mouse 113
Conclusions 114
References 114
Further Reading 117

Section III: Precision Control 119

8 Coordination 121
Precise Ocular Coordination 122
Coordinating the Eyes and the Head 126
Error Correction for Limb Movements 127
Planning for Multiple Joints 129
Internal Models Revisited 132

Conclusions 134
References 134
Further Reading 137

9 Balance and Locomotion 139
Cerebellar Ataxia 140
Signals from the Inner Ear 142
Coordinating Locomotion 146
Navigation 148
Conclusions 150
References 150
Further Reading 152

10 Timing 153
Timing Using Discharge Rates 154
Timing Using Synchronous Firing 161
Conclusions 165
References 166
Further Reading 168

Section IV: Interpreting the World 169

11 Intelligence and Language 173
General Intelligence 175
Executive Function 177
Problem-solving 181
Speech and Language 183
Possible Mechanisms 187
Conclusions 188
References 188
Further Reading 191

12 Sensing, Feeling, and Interacting 193
Sensory Perception 194
Attending to the World 198
Prediction 200
Mental Imagery 202
Social Skills 204
Conclusions 208
References 208
Further Reading 211

Summary: What does the cerebellum do? 213
Index 215

Section I

The Neuronal Machine

The Cerebellum: Learning Movement, Language, and Social Skills, First Edition. Dianne M. Broussard.
© 2014 John Wiley & Sons, Inc. Published 2014 by John Wiley & Sons, Inc.

此为试读,需要完整PDF请访问: www.ertongbook.com

1 Structure and Physiology

ANATOMY OF THE CEREBELLAR CORTEX

Even the most primitive vertebrates have a cerebellum. For example, the cyclostomes (hagfish and lampreys) have a cerebellum, even though—like other fish—they do not have a cerebral cortex.

The cerebellum may have first appeared as a computational device for the lateral line systems of fish.Lateral lines are rows of tiny hair cells on the skin of fish that detect rocks, fish, and other solid objects. Without their lateral line organs, fish collide with obstacles (Sarnat & Netsky 1974). While swimming alongside a wall, for example, the fish's movement is continually adjusted to maintain a constant distance, based on signals from the lateral lines. Both the lateral line nerves and the central nuclei associated with them send axonal projections into the cerebellum. The purpose of the first cerebellum may have been to carry out computations that allowed fish to use the sensory feedback from their lateral lines to guide swimming.

The cerebellum of cyclostomes works with a very simple structure. It contains only two types of neurons: the tiny and very numerous granule cells, and the large Purkinje cells (P-cells), with their extensive dendritic arbors. The dendrites of each P-cell branch within a flattened, nearly planar field in the molecular layer. Granule cells terminate on and excite the P-cells. P-cells are the only neurons whose axons leave the cortex. Unlike most other large projection neurons of the brain, they inhibit their target neurons.

Both granule cells and P-cells receive afferent input. Granule cells are innervated by the mossy fibers, so called because their axon terminals resemble miniature branches and leaves of moss. In cyclostomes, mossy fibers originate from the lateral line and vestibular nuclei. The P-cells have direct input from the ivy-like climbing fibers, whose cell bodies are located in the inferior olivary nuclei of the brainstem.

Throughout vertebrate evolution, the cerebellar cortex has kept these primitive features and added more. In humans, the cerebellar cortex has three layers (Figure 1.1): the molecular layer, which is a surface layer

The Cerebellum: Learning Movement, Language, and Social Skills, First Edition. Dianne M. Broussard.
© 2014 John Wiley & Sons, Inc. Published 2014 by John Wiley & Sons, Inc.

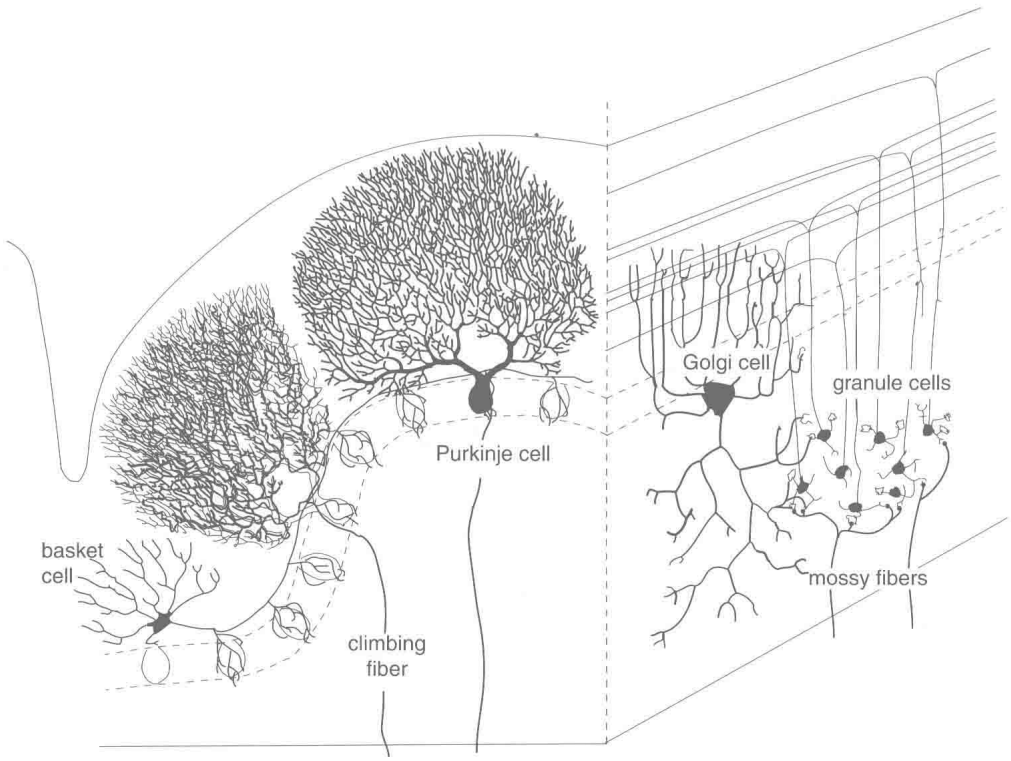


Figure 1.1 Human cerebellar cortex. A P-cell, a climbing fiber, and a basket cell are shown in the sagittal plane. Golgi and granule cells and mossy fibers are shown in the coronal plane. The dashed lines indicate the P-cell layer. The axon of the basket cell is shown extending in the sagittal plane and surrounding the cell bodies of several P-cells. See text for other details.

containing mostly axons; the P-cell layer; and the granular layer. The granular layer contains between 10^{10} and 10^{11} granule cells in humans (Braitenberg & Atwood 1958).[1]

The axons of granule cells extend from the granule cell layer, through the P-cell layer, and into the molecular layer where they bifurcate, each branch making a right-angle turn. The branches, which are thin and unmyelinated, are called parallel fibers. They extend for several millimeters, terminating extensively on the P-cell dendrites and releasing glutamate. Input from the mossy fibers can excite P-cells through the granule cells and parallel fibers. The rectangular lattice formed by the P-cell dendritic arbors and the parallel fibers suggests an efficient device for processing and/or storing information.

[1]This astounding number represents most of the neurons in the brain. Although it has been questioned, these authors were very careful in their methodology.

The climbing fibers originate from the inferior olive. In general, each P-cell receives input from only one climbing fiber, although there are exceptions (Nishiyama & Linden 2004). Climbing fibers usually extend through the entire thickness of the molecular layer, twining around the dendrites of the P-cell.

In mammals, the cerebellar cortex contains inhibitory interneurons, that form another link between the granule cells and the P-cells. These are the basket cells and the stellate cells. The basket cell is named for the structure of its terminal, which is a giant synapse, also known as the "pinceau". One pinceau surrounds the soma of each P-cell, secreting GABA and inhibiting the initial segment of the axon as well as the soma itself. The long axons of the basket cells extend parallel to the P-cell dendritic arbors, at right angles to the parallel fibers. The discharge pattern of a basket cell effectively sculpts the discharge patterns of each P-cell that it innervates. Stellate cells also inhibit P-cells, but they terminate on the dendrites and are less effective.

Basket cells and stellate cells also receive collaterals from the climbing fibers. This means that each excitatory input to the P-cell is accompanied by an inhibitory input that is derived from it (Figure 1.2).

Only one type of inhibitory interneuron, the very large Golgi cell, terminates on granule cells. The Golgi cell closes an inhibitory feedback loop. As a result, like P-cells, granule cells receive both excitatory and inhibitory inputs.

In addition to mossy fibers, which are glutamatergic and terminate exclusively in the granular layer, and climbing fibers (also glutamatergic), input pathways to the cerebellum arise from the locus coeruleus (adrenergic neurons) and raphe nuclei (serotonergic neurons). These axons terminate directly on P-cells.

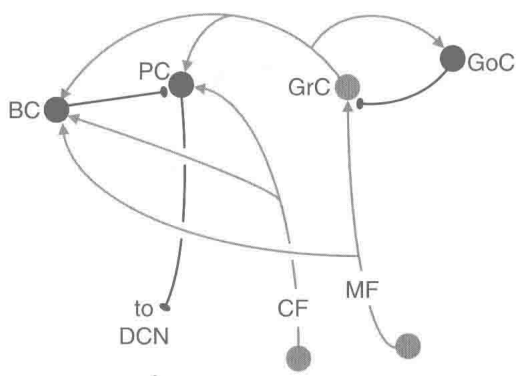


Figure 1.2 A simplified diagram of the connections among neurons in the cerebellar cortex. Black cells and round terminals are inhibitory. Gray cells and arrows are excitatory. PC, Purkinje cell; BC, basket or stellate cell; GoC, Golgi cell; GrC, granule cell; MF, mossy fiber; CF, climbing fiber; DCN, deep cerebellar nucleus.

PHYSIOLOGY OF THE CEREBELLAR CORTEX

What do all of these parts do? Over the years, neurophysiologists have carried out hundreds of studies of the cerebellar cortical circuit, with the goal of answering this question. At least one important principle has held up over time: the close relationship between the vine-like climbing fiber and the P-cell is of primary importance to cerebellar function. Because the climbing fiber has a large number of glutamatergic terminals on the P-cell, each action potential in the climbing fiber strongly depolarizes the dendritic arbor. This strong synaptic activation, along with a "resurgent" sodium current (Raman & Bean 1997), results in an action potential in the P-cell that has not one but several peaks (the "complex spike"). On the cellular level, complex spikes are necessary for cerebellar learning. In at least some cases, climbing fibers bring information about errors into the cortex.

In adult mammals, most P-cells are innervated by only one climbing fiber, and in fact, this pattern of innervation is required for certain kinds of learning (Kimpo & Raymond 2007). But climbing fibers fire infrequently, usually evoking 10 or fewer complex spikes per second. Meanwhile, the P-cell fires "simple spikes" (ordinary action potentials) steadily at up to 100 spikes per second or more, allowing it to encode rapid sensory and motor events. The steady stream of simple spikes is the main output of the cerebellar cortex, but as we shall see, complex spikes can affect the stream.

Parallel fibers: many weak inputs

The sheer number of synapses that connect granule cell axons, especially the long parallel fibers, with P-cells suggests that the mossy-fiber input pathway must be important. There are roughly 150,000 synapses from parallel fibers on each P-cell, and we each have over 10 million P-cells. This arrangement provides enormous computational power. It has the potential to encode a tremendous number of different components of motor patterns, for example.

But despite these impressive numbers, it is clear that the parallel fiber–P-cell (PF–PC) circuit is not the only contributor to cerebellar signal processing in mammals, and it may not even be the most important contributor. For one thing, P-cells can generate simple spikes at a steady rate on their own, without any synaptic input (Hounsgaard & Yamamoto 1979). This "spontaneous" firing likely occurs because the resurgent sodium current does not completely inactivate. As a result, the resting potential of the P-cell is above the threshold for firing (Raman & Bean 1997). Spontaneous firing can be modulated by the many synaptic inputs

to the P-cell, but inhibitory inputs are likely to be more useful for this kind of modulation than excitatory ones.[2]

Climbing fibers and inhibitory interneurons

Another important contributor to P-cell discharge patterns is the climbing-fiber input. At the same time that it causes complex spikes, the climbing-fiber input actually *decreases* the rate of simple-spike firing by the same P-cell (Montarolo *et al.* 1982). In most behavioral paradigms, complex spikes and simple spikes show opposing responses, with complex spikes decreasing while simple spikes increase their discharge rates, and vice versa. In fact, the pattern of complex-spikes seems to *determine* the simple-spike responses of some P-cells to sensory stimuli (Barmack & Yakhnitsa 2003). Although we do not know exactly how this works, evidence indicates that at least two mechanisms may contribute: the activation of calcium-activated potassium channels in P-cells (McKay *et al.* 2007), and the activation of stellate and basket cells (Barmack & Yakhnitsa 2011). In at least some cerebellar regions, the stellate and basket cells control whether P-cells will increase or decrease their simple-spike firing rates during particular sensory stimuli (Barmack & Yakhnitsa 2008).

Both granule cells and P-cells do more than just add up their synaptic inputs. P-cells sometimes end up responding to sensory and motor events in a similar way to the mossy fibers, but sometimes they do not. In fact, the responses of P-cells and mossy fibers can end up being opposites (Barmack & Yakhnitsa 2008). This situation is not as strange as it first seems. Each parallel fiber provides one or a few relatively minor inputs to the P-cell. These inputs arrive on the dendritic spines, which are electrically quite distant from the spike generator of the P-cell. Furthermore, the P-cell is spontaneously active, so after each spike it may reach threshold again within a few milliseconds, whether or not it receives any depolarizing synaptic input. On the other hand, inhibitory inputs can sculpt the spontaneous activity of the P-cell. The basket cell actually terminates on the soma and the proximal axon, and override the more distal parallel-fiber inputs. It is clear that the basket cell is a key player in determining how P-cells will respond to sensory and motor events.

[2]This is because inhibitory inputs open (usually) chloride channels, which shunts postsynaptic excitatory currents and also intrinsically-generated currents. This is roughly analogous to a short in electrical wiring and has a similarly powerful effect.

此为试读,需要完整PDF请访问: www.ertongbook.com