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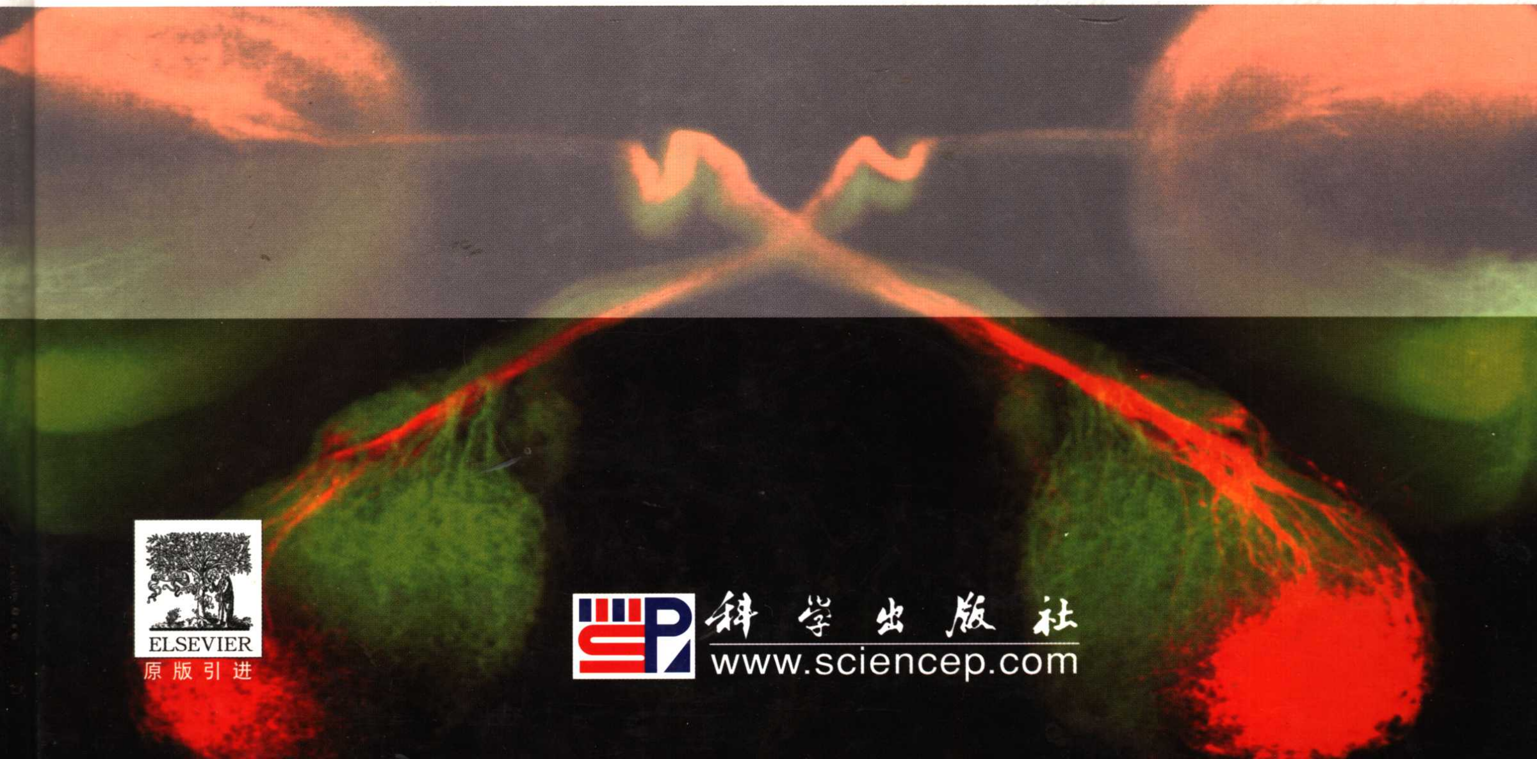
Development of the Nervous System

神经系统发育

（第二版）

Dan H. Sanes, Thomas A. Reh, William A. Harris



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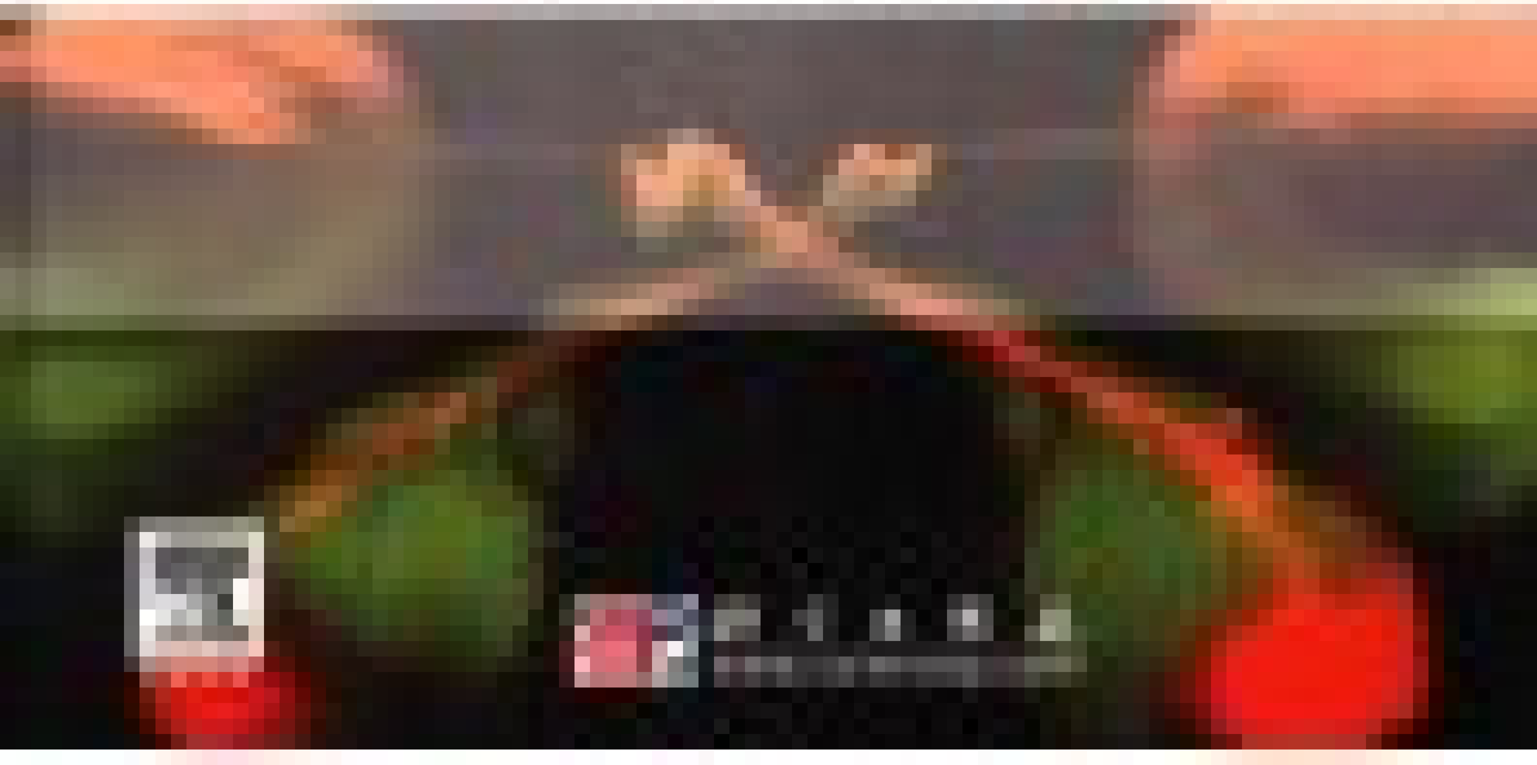

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To our families

第一版序

众所周知人脑是我们已知世界中最为复杂的一个物体，数以十亿计的细胞和细胞间数以万亿计的各种联系是其中最为奥妙的部分。探寻神经系统中细胞产生感觉、行为以及高级精神活动的方式已经成为科学界中成果最为丰硕的一个领域。但是，神经科学家们已经意识到他们研究的是一个不断发生着变化的目标：生长和改变与脑的功能是一个统一的整体，并且只有在此统一的基础上我们才能研究其它任何与之相关的东西。行为胚胎学家 George Coghill 指出，“人体实际上就是一部机器，但是这部机器在其有限的生命、感知和成长中在不断自我创造和自我运行”。因此，为了认识脑，我们需要了解这部机器是怎样起源以及在其一生的时间中它是怎样变化的。

脑的构成是一系列发育阶段的整合体，由最初少量胚胎细胞成为神经前体细胞开始，随着神经细胞之间联系的形成以及它们电活动特征的显现，到脑开始处理信息并且介导行为功能。虽然一些潜在的环路在胚胎发育期就已经构建在神经系统中，但脑与这个世界的联系却是不断更新的，并逐步改变着脑的功能构筑。这些变化发生的机制似乎是一个渐进的过程，它在发育过程中对脑的结构进行塑造。因此，本书涵盖了这些发育阶段的每一步骤，所以涉及的面相对广泛。

理解神经系统的发育对广大生物学家来说有着重要意义，对发育的研究引领我们看到许多生物体在进化中的联系。上世纪关于种系发生和个体发生的法则已经被目前更深层次的理解所代替，即进化发生的方式会受到发育中变化的影响。当然，脑也毫无例外地遵循这样的原则。因此，我们认为，理解发育的进程怎样随时间而改变将有助于深入理解令我们更加人性化的进化过程。

本书的目的就是为高年级学生或那些有生物学背景的研究工作者提供一个神经发育过程的纲要，这与广泛的文献综述在目的上是完全不同的。在最近一次的 MEDLINE 搜索中发现（以神经/神经元/神经的和发育/胚胎学/成熟为检索词），从 1966 年到 1999 年，在神经发育领域发表的论文已达到 56 840 篇，而我们只阅读了这些文章和 1966 年以前的数千篇文献中的一小部分。为了解决这个实际问题，我们参考了权威的书籍、最新的文献综述和会议论文，并对我们在本书中选用的实验都进行了咨询。即便如此，疏漏也在所难免。因此，有兴趣的学生可以通过查阅文献和综述对某些部分作更加详细的了解。另一个需要考虑的就是，我们是在分子生物学的变革开始后来编写这本高年级生物学教材的，所以涉及的主题大部分都包括了分子的特性。除此以外，关于某一族分子最有启发性的实验在非神经组织中常常都已经进行过了，即使我们仅选择一些在神经系统中作用较明确的基因和蛋白质，也可能会使大多数章节看上去就像一长串单词的堆砌。因此，在给学生最新信息和努力抓住他们兴趣的两者之间，我们找到一个平衡点来写这本书，把最新的综述文章作为我们写书时的附录供学生参考，而避免罗列繁多的分子家族。

本书在写作过程中得到了许多科学家的大力支持，他们是（按照字母顺序）：Chiye Aoki，Michael Bate，Olivia Bermingham-McDonogh，John Bixby，Sarah Bottjer，Martin Chalfie，Hollis Cline，Martha Constantine-Paton，Ralph Greenspan，Voker Hartenstein，Mary Kintner，Sue McConnell，Ilona Miko，Ronald Oppenheim，Thomas Parks，David Raible，Henk Roelink，Edwin Rubel，John Rubenstein，David Ryugo，Nancy Sculerati，Carla Shatz，and Tim Tully。

（蔡文琴　译）

第二版序

众所周知人脑是我们已知世界中最为复杂的一个物体，数以十亿计的细胞和细胞间数以万亿计的各种联系是其中最为奥妙的部分。尽管我们对于脑的认识还远远不够，但是研究组成神经系统的神经元和胶质细胞产生感觉、行为和高级精神活动的方式已经成为科学研究中成果最丰硕的领域。然而，越来越多的神经科学家意识到他们研究的是一个不断发生变化的目标，它的改变与脑的功能是一个整体，构成了学习、感知和行为的基础。因此，为了认识脑的功能，我们必须理解这些神经环路是如何发生的，以及它们在成熟过程中以怎样的方式被调节。Santiago Ramón y Cajal是现代神经科学的奠基人之一，他之所以可以在研究神经系统细胞构成方面获得杰出的成就，在很大程度上是因为他的研究目标是胚胎脑，换句话说，他选择的研究对象是“年轻的树，正处于成长阶段，而不是已经完全长成而不再变化的森林”。

脑的构成是一系列发育阶段的整合体，由最初少量胚胎细胞成为神经前体细胞开始，到接近行为出现为止，这就是本书所涵盖的内容。脑与世界的联系总是在不断地更新，同时这些更新也改变着脑内突触的联系。这种变化发生的机制似乎是一个渐进的过程，它在发育过程中对脑的结构进行塑造。

对发育的研究使我们可以洞察生物体之间在进化中的关系。上世纪关于种系发生和个体发生的法则已经被目前更深层次的理解所代替，即进化发生的方式会受到发育中变化的影响。当然，脑也毫无例外地遵循这样的原则。因此，我们认为，理解发育的进程怎样随时间而改变将有助于深入理解令我们更加人性化的进化过程。

本书的目的就是为高年级学生和有一些生物学背景的研究者提供一个关于神经发育过程的纲要，这与广泛的文献综述在目的上是完全不同的。在第一版中，我们已经提到本领域在1966年到1999年期间约有54 000篇论文发表。而在已经过去的四年中又有25 000篇论文发表（以神经/神经元/神经的和发育/胚胎学/成熟以及2000～2004为检索词）。因为我们不可能把所有研究中的精彩部分完全囊括，所以在给学生最新信息和努力抓住他们兴趣的两者之间，我们找到一个平衡点来写这本书，把最新的综述文章作为我们写书时的附录供学生参考，而避免罗列繁多的分子家族。有兴趣的学生可以通过查阅文献和综述对某些部分作更加详细的了解。

本书在讨论和编辑过程中得到了以下这些人员的帮助，他们是Chiye Aoki，Michael Bate，Carla Shatz，Ford Ebner，Edward Gruberg，Christine Holt，Lynne Kiorpes，Vibhakar Kotak，Tony Movshon，Ron Oppenheim，Sarah Pallas，Sheryl Scott，Tim Tully，and Lance Zirpel。

最后还要感谢本书的编辑Johannes Menzel，衷心感谢他的帮助、建议和鼎力支持。

Dan H. Sanes
Thomas A. Reh
William A. Harris
2005年7月

（蔡文琴　译）

Preface to the First Edition

The human brain is said to be the most complex object in our known universe, and the billions of cells and trillions of connections are truly wonders of enormous proportions. The study of the way that the cellular elements of the nervous system work to produce sensations, behaviours, and higher order mental processes has become a most productive area of science. However, neuroscientists have come to realize that they are studying a moving target: growth and change are integral to brain function and form the very basis by which we can learn anything about it. As the behavioral embryologist George Coghill pointed out, "Man is, indeed, a mechanism, but he is a mechanism which, within his limitations of life, sensitivity and growth, is creating and operating himself." To understand the brain, then, we need to understand how this mechanism arises and the ways in which it can change throughout a lifetime.

The construction of the brain is an integrated series of developmental steps, beginning with the decision of a few early embryonic cells to become neural progenitors. As connections form between nerve cells and their electrical properties emerge, the brain begins to process information and mediate behaviors. Some of the underlying circuitry is built into the nervous system during embryogenesis. However, interactions with the world continuously update and adapt the brain's functional architecture. The mechanisms by which these changes occur appear to be a continuation of the processes that sculpt the brain during development. Since the text covers each of these developmental steps, it is relatively broad in scope.

An understanding of the development of the nervous system has importance for biologists in a larger context. Studies of development have led to insights into the evolutionary relationships among organisms. The dogma of phylogeny and ontogeny of the last century has been superseded by a deeper understanding of the ways in which evolutionary change can be effected through changes in development. The brain is no exception to these rules. We should expect that insight into the evolution of that which makes us most human will be gained from an appreciation of how developmental processes are modified over time.

The goal of this text is to provide a contemporary overview of neural development for undergraduate students or those who have some background in the filed of biology. This intent is not compatible with a comprehensive review of the literature. A recent MEDLINE search of publications in the field of neural development [(neural or neuron or nervous) and (development or embryology or maturation)] yielded 56,840 papers published between 1966 and 1999. We admit, up front, to having read only a fraction of these papers or of the thousands that were published before 1966. As a practical matter, we made use of authoritative books, contemporary review articles, hallway conversations, and e-mail consultations to select the experiments that are covered in our text. Even so, we expect that important contributions have been missed inadvertently. Therefore, advanced students will find themselves quickly turning to specialized texts and reviews. Another compromise that comes from writing an undergraduate biology book well after the onset of the revolution in molecular biology is that all subjects now have a rather broad cast of molecular characters. In addition, the most instructive experiments on a particular class of molecules have often been performed on nonneural tissue. Even if we chose to cover only the genes and proteins whose roles have been best characterized in the nervous system, most chapters would run the risk of sounding like a (long) list of acronyms. Therefore, we charted a compromise between the need to update students and our strong inclination to hold their attention. The book does not contain exhaustive lists of molecular families, and the most current articles must serve as an appendix to our text.

Among the many scientists who helped us through discussions, unpublished findings, or editorial comment are (in alphabetical order) Chiye Aoki, Michael Bate, Olivia Bermingham-McDonogh, John Bixby, Sarah Bottjer, Martin Chalfie, Hollis Cline, Martha Constantine-Paton, Ralph Greenspan, Voker Hartenstein, Mary Beth Hatten, Christine Holt, Darcy Kelley, Chris Kintner, Sue McConnell, Ilona Miko, Ronald Oppenheim, Thomas Parks, David Raible, Henk Roelink, Edwin Rubel, John Rubenstein, David Ryugo, Nancy Sculerati, Carla Shatz, and Tim Tully.

Preface to the Second Edition

The human brain—perhaps the most complex object in our universe—is composed of billions of cells and trillions of connections. It is truly a wonder of enormous proportions. Although we are far from a thorough understanding of our brains, study of the way that the cellular constituents of the nervous system, the neurons and glia, work to produce sensations, behaviors, and higher order mental processes has been a most productive area of science. However, more and more, neuroscientists are realizing that we are studying a moving target-growth and that changes are integral to brain function, forming the very basis for learning, perception, and performance. To comprehend brain function, then, we must understand how the circuits arise and the ways in which they are modified during maturation. Santiago Ramón y Cajal, one of the founders of modern neuroscience, was able to make his remarkable progress in studies of the cellular makeup of the nervous system in large part because of his work with the embryonic brain, choosing to study "the young wood, in the nursery stage . . . rather than the . . . impenetrable . . . full grown forest."

The construction of the brain is an integrated series of developmental steps, starting with the decision of a few early embryonic cells to become neural progenitors and nearing completion with the emergence of behavior, which is the scope of this book. Interactions with the world continuously update and adapt synaptic connections within the brain, and the mechanisms by which these changes occur are fundamentally a continuation of the same processes that sculpted the emerging brain during embryogenesis.

Studies of development have also led to insights about the evolutionary relationships among organisms. The dogma of phylogeny and ontogeny of the last century has been superseded by our current deeper understanding of the ways in which evolutionary change can be effected through changes in development. The brain is no exception to these rules, and we can expect that much insight into the evolution of that which makes us most human will be gained from an appreciation of how developmental processes are modified over time.

The goal of this text is to provide a contemporary overview of neural development both for undergraduate students and for those who have some background in the field of biology. This intent is not compatible with a comprehensive review of the literature. In the first edition, we noted that there were about 54,000 papers published in this field between 1966 and 1999. Another 25,000 have appeared during the past 4 years (using the search string "neural or neuron or nervous" and "development or embryology or maturation" and 2000:2004). We charted a compromise between the need to update students and our strong inclination to hold their attention. The book does not contain exhaustive lists of molecular families, and the most current review articles must serve as an appendix to our text. Since the text does not encompass many exciting areas of research, students will find themselves quickly turning to specialized texts and reviews.

Among those who helped us through discussion and editorial comment are: Chiye Aoki, Michael Bate, Carla Shatz, Ford Ebner, Edward Gruberg, Christine Holt, Lynne Kiorpes, Vibhakar Kotak, Tony Movshon, Ron Oppenheim, Sarah Pallas, Sheryl Scott, Tim Tully, and Lance Zirpel.

Finally, we acknowledge our editor, Johannes Menzel, with particular gratitude, for his help, advice, and perseverance.

Dan H. Sanes
Thomas A. Reh
William A. Harris
July 2005

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