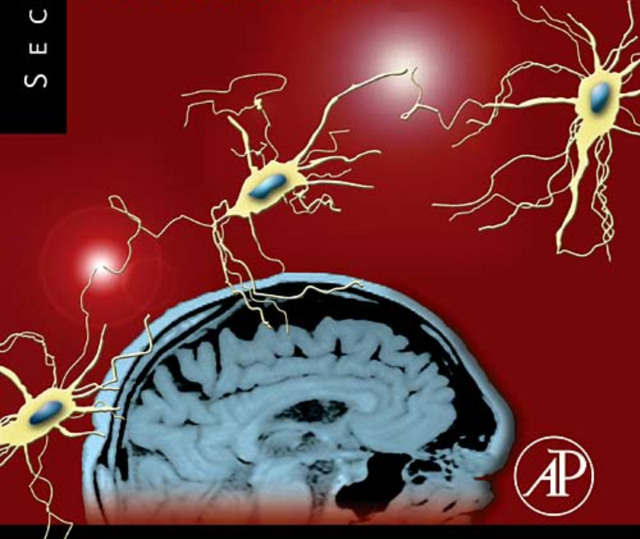
NEUROBIOLOGY OF LEARNING AND MEMORY

SECOND EDITION

EDITED BY

JOE MARTINEZ

RAYMOND KESNER



Neurobiology of Learning and Memory

This page intentionally left blank

Neurobiology of Learning and Memory

SECOND EDITION

Edited by

RAYMOND P. KESNER

Department of Psychology
University of Utah
Salt Lake City, Utah

JOE L. MARTINEZ, JR.

Division of Life Sciences
The University of Texas at San Antonio
San Antonio, Texas

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
Academic Press is an imprint of Elsevier

Publisher: Nikki Levy
Senior Developmental Editor: Barbara Makinster
Marketing Manager: Patricia Howard
Project Manager: Jeff Freeland
Cover Designer: Eric DeCicco
Compositor: SNP Best-set Typesetter Ltd., Hong Kong
Printer/Binder: Hing Yip Printing Co., Ltd.

Academic Press is an imprint of Elsevier
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
Linacre House, Jordan Hill, Oxford OX2 8DP, UK

Library of Congress Cataloging-in-Publication Data
Neurobiology of learning and memory / edited by Raymond P. Kesner, Joe L. Martinez, Jr. — 2nd ed.
p. cm.
Includes bibliographical references (p.).
ISBN-13: 978-0-12-372540-0 (alk. paper)
ISBN-10: 0-12-372540-2 (alk. paper)
1. Learning — Physiological aspects. 2. Memory — Physiological aspects. 3. Neurobiology. I. Kesner, Raymond P. II. Martinez, Joe L.
QP408.N492 2007

612.8′2 — dc22

2006051913

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

ISBN: 978-0-12-372540-0

For information on all Academic Press publications
visit our Web site at www.books.elsevier.com

Printed in China
07 08 09 10 11 12 10 9 8 7 6 5 4 3 2 1

This book is dedicated to our wives,
Drs. Laya Kesner and Kimberly Smith-Martinez.

This page intentionally left blank

Contents

2 *Developmental Approaches to the Memory Process*

Julie A. Markham, James E. Black, and William T. Greenough

3 *Genetics in Learning and Memory*

Yalin Wang, Josh Dubnau, Tim Tully, and Yi Zhong

4 *Gene Expression in Learning and Memory*

Joe L. Martinez, Jr., Kenira J. Thompson, and Angela M. Sikorski

5 *Mnemonic Contributions of Hippocampal Place Cells*

Sherri J. Y. Mizumori, D. M. Smith, and C. B. Puryear

9 *The Medial Temporal Lobe and Memory*

Alison R. Preston and Anthony D. Wagner

10 *Bootstrapping Your Brain: How Interactions Between the Frontal Cortex and Basal Ganglia May Produce Organized Actions and Lofty Thoughts*

Earl K. Miller and Timothy J. Buschman

11 *Role of the Striatum in Learning and Memory*

Michael E. Ragozzino

12 *Neural Systems Involved in Fear and Anxiety Based on the Fear-Potentiated Startle Test*

Michael Davis

13 *Cerebellar Learning*

Tatsuya Ohyama and Michael D. Mauk

Part III Applications of the Importance of Learning and Memory to Applied Issues

This page intentionally left blank

Contributors

Numbers in parentheses indicate the chapter contributed by authors.

Carol A. Barnes (15)
Arizona Research Labs
Division of Neural Systems, Memory and Aging
University of Arizona
Tucson, AZ 85724

James E. Black (2)
Department of Psychiatry
Southern Illinois School of Medicine
Springfield, IL 62794

Timothy J. Buschman (10)
Picower Institute for Learning and Memory
RIKEN-MIT Neuroscience Research Center
Department of Brain and Cognitive Sciences
Massachusetts Institute of Technology
Cambridge, MA 02142

Michael Davis (12)
Department of Psychiatry
Emory University School of Medicine
Atlanta, GA 30322

Josh T. Dubnau (3)
Cold Spring Harbor Laboratory
Cold Spring Harbor, NY 11724

Paul E. Gold (7)
Departments of Psychology and Psychiatry
Neuroscience Program
Institute for Genomic Biology
University of Illinois
Champaign, IL 61820

William T. Greenough (2)
Beckman Institute
University of Illinois
Urbana, IL 61801

Stephen C. Heinrichs (17)
Department of Psychology
Boston College
Chestnut Hill, MA 02467

Peter W. Kalivas (14)
Department of Physiology
Medical University of South Carolina
Charleston, SC 29425

Raymond P. Kesner (8)
Psychology Department
University of Utah
Salt Lake City, UT 84112

Donna L. Korol (7)
Department of Psychology
Neuroscience Program
Institute for Genomic Biology
University of Illinois
Champaign, IL 61820

Ryan T. LaLumiere (14)
Department of Neurosciences
Medical University of South Carolina
Charleston, SC 29425

Julie A. Markham (2)
Beckman Institute
University of Illinois
Urbana, IL 61801

Joe L. Martinez, Jr. (4)
Biology Department
University of Texas
San Antonio, TX 78249

Michael D. Mauk (13)
Department of Neurobiology and Anatomy
University of Texas Medical School
Houston, TX 77030

Earl K. Miller (10)
Picower Institute for Learning and Memory
Riken-MIT Neuroscience Research Center
Department of Brain and Cognitive Sciences
Massachusetts Institute of Technology
Cambridge, MA 02139

Sherri J. Y. Mizumori (5)
Department of Psychology
University of Washington
Seattle, WA 98195

Tatsuya Ohyama (13)
Department of Neurobiology and Anatomy
University of Texas Medical School
Houston, TX 77030

Marsha R. Penner (15)
Division of Neural Systems, Memory and Aging
University of Arizona
Tucson, AZ 85724

Alison R. Preston (9)
Department of Psychology
Neurosciences Program
Stanford University
Stanford, CA 94305

Corey B. Puryear (5)
Department of Psychology
University of Washington
Seattle, WA 98195

Michael E. Ragozzino (11)
Department of Psychology
University of Illinois
Chicago, IL 60607

Edmund T. Rolls (6)
Department of Experimental Psychology
University of Oxford
Oxford OX1 3UD, United Kingdom

Mark R. Rosenzweig (1)
Department of Psychology
University of California
Berkeley, CA 94720

Angela M. Sikorski (4)
Department of Biology
University of Texas
San Antonio, TX 78249

D. M. Smith (5)
Department of Psychology
University of Washington
Seattle, WA 98195

Kenira J. Thompson (4)
Department of Physiology
Ponce School of Medicine
Ponce, PR 00732

Tim Tully (3)
Cold Spring Harbor Laboratory
Cold Spring Harbor, NY 11724

Anthony D. Wagner (9)
Department of Psychology
Neurosciences Program
Stanford University
Stanford, CA 94305

Yalin Wang (3)
Cold Spring Harbor Laboratory
Cold Spring Harbor, NY 11724

Gary L. Wenk (16)
Department of Psychology
Ohio State University
Columbus, OH 43210

Yi Zhong (3)
Cold Spring Harbor Laboratory
Cold Spring Harbor, NY 11724

This page intentionally left blank

Preface

Graduate students interested in the neurosciences with a special interest in behavior are the intended audience. The major aim of this book is to present up-to-date information on the neurobiology of learning and memory based on multiple levels of analysis, contributions of multiple brain regions, systems that modulate memory and applications to aging, drugs of abuse, neurodegenerative diseases, and models of enhancement of memory. The emphasis will be on both animal and human studies.

The first section of the book covers different approaches to understanding the neurobiological basis of learning and memory. More specifically, there is an excellent introduction to the history of the neurobiology of learning and memory incorporating information from all of the contributing authors (Rosenzweig). With three chapters the book covers the developmental and genetic contributions to memory. This topic is becoming very important with the discovery of a variety of genetic tools to examine the role of specific genes and their contribution to learning, memory formation, and memory storage and retrieval (Markham, Black, and Greenough; Wang, Dubnau, Tully, and Zhong; and Martinez, Thompson, and Sikorski). Plasticity as it relates to memory has played a critical role in delineating the cellular properties of neurons that can maintain information over time (Mizumori and Smith). There is one chapter that emphasizes the role of place cells in the hippocampus and interconnected neural circuits based primarily on an electrophysiological analysis of cellular changes associated with learning and memory (Mizumori and Smith). There is one chapter that will cover a new area of theoretical importance for all of the different brain regions, namely the use of computational models to aid in providing a new theoretical approach to understand the processes that subserve memory (Rolls). Finally, in this section there is a chapter that covers the influence of hormonal processes on learning and memory (Korol and Gold).

The second section of the book covers the contribution of neural systems in mediating learning and memory. Since there are many brain regions associated with the processing of information of importance to learning and memory, six chapters outline a multiple system and multiple processes approach to understanding the complexity of information processing resulting in memory encoding, storage, and retrieval. The chapters deal with the following neural substrates, namely the medial temporal lobe, the frontal lobes, amygdala, basal ganglia, and cerebellum and cover experimental results and theoretical ideas based on research with humans, monkeys, and rats. Multiple approaches and techniques aimed at studying these brain regions are presented including, neuroanatomy, electrophysiology, lesion, pharmacology, fMRI, behavior, and cognitive analysis (Kesner; Preston and Wagner; Miller and Buschman; Ragozzino; Davis; Ohyama and Mauk).

The third section of the book emphasizes applications of the importance of learning and memory to applied issues. There are four chapters that provide a connection between all the previous chapters and important applications of the basic empirical findings to real world issues. The chapters cover issues of reward and drugs of abuse, the effects of aging on memory, the importance of studying neurodegenerative diseases from both the molecular and treatment approaches to memory and a final look at our ability to enhance memory (Balmier and Kalivas; Barnes and Penner; Wenk; Heinrichs).

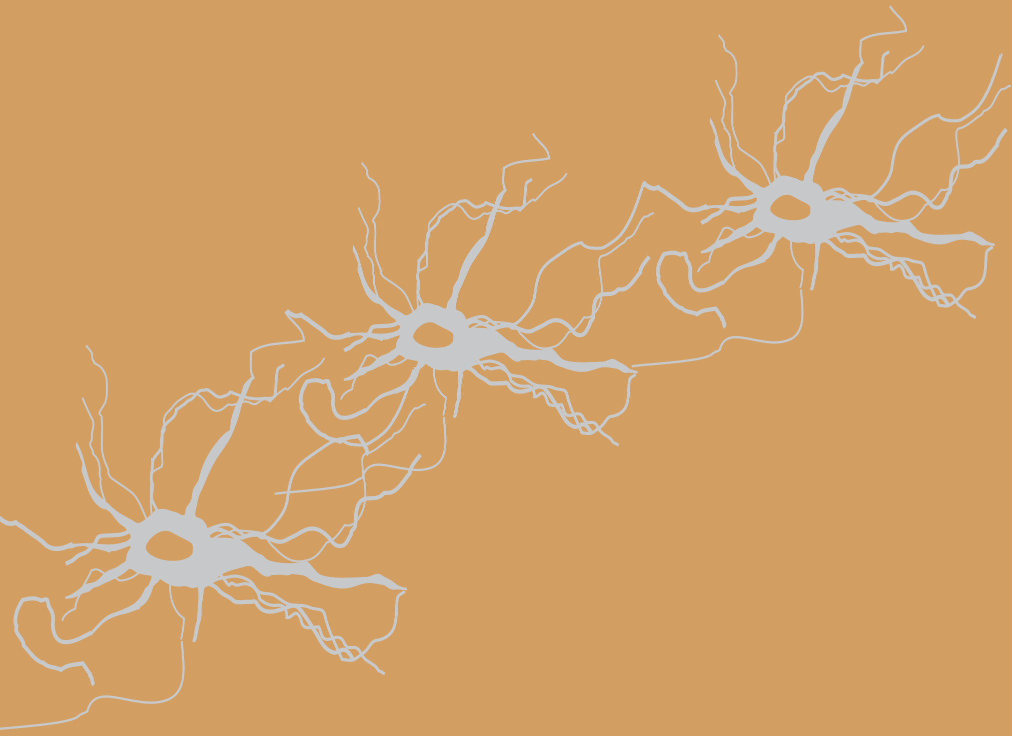
The emphasis of each chapter will be on the presentation of the latest and most important research on the topic, the development of a theoretical perspective, and providing an outline that will aid a student in understanding the most important concepts presented in each chapter.

Ray Kesner

Joe Martinez

Part I

Approches to Understanding the Neurobiological Basis of Learning and Memory



This page intentionally left blank

CHAPTER 1

Historical Perspective

Mark R. Rosenzweig
Department of Psychology, University of California, Berkeley, CA 94720

I. INTRODUCTION

The following chapters review recent and current research on many important aspects of the neurobiology of learning and memory. This chapter gives some historical perspective to this active field. Having participated in this research for half a century, I am happy to share information, interpretations, and insights about this productive multidisciplinary area.

In antiquity, speculation about mechanisms of memory took the form of metaphors, and metaphors of memory continue to be proposed in the present day. By the last quarter of the nineteenth century, scientific hypotheses and investigations of memory and its mechanisms began to be made, and it appeared that progress would be rapid. Research on neurobiological mechanisms of memory appeared to stall, however, and by the middle of the twentieth century, some thinkers despaired about the possibility of progress in this apparently intractable field. But shortly after midcentury, research and theory took off again, and rapid progress has continued to this day.

Neurobiology of Learning and Memory, Second Edition

II. METAPHORS OF MEMORY

Concern about memory and its mechanisms goes far back in recorded history. An ancient Egyptian legend, related by the Greek philosopher Plato (427–347 BCE) in his *Phaedrus*, told that Thoth, the god of knowledge, offered the gift of writing to King Thamus of Egypt. The king was reluctant to accept the gift, expressing the fear that writing would cause forgetfulness because people would no longer exercise their memories but tend to rely instead on external written characters.

Thinkers in antiquity speculated about the mechanisms of memory and suggested metaphors for them. A widespread metaphor for memory was writing on a tablet coated with wax. The god Thoth was often depicted writing on such a tablet. As Draaisma notes in his book *Metaphors of Memory: A History of Ideas About the Mind* (2000), the classic passage on the wax tablet as the metaphor for memory appears in Plato's (1987) *Theaetetus*. In this dialogue, Socrates suggests:

> [O]ur minds contain a wax block, which may vary in size, cleanliness and consistency in different individuals, but in some people is just right. . . . [W]henever we want to remember something we've seen or heard or conceived on our own, we subject the block to the perception or the idea and stamp the impression into it. . . . We remember and know anything imprinted, as long as the impression remains in the block; but we forget and do not know anything which is erased or cannot be imprinted (pp. 99–100).

This wax tablet, wrote Plato, was a gift of Mnemosyne, the goddess of memory in the Greek pantheon and mother of the muses. We still acknowledge this goddess when we speak of mnemonic devices.

The metaphor of the wax tablet returned at greater length and in greater detail in the work of Aristotle (384–322 BCE), the pupil of Plato. Aristotle suggested that in the case of illness that affected memory, the consistency of the wax would be too loose, so no clear image could be stamped on it, just as no impression would be formed if a seal were to impinge on running water. He proposed that this is also why young children and old people have poor memories. They are in a state of flux, the former because of their growth, the latter because of their decay (see ref. in Draaisma, 2000, p. 46). The close association of memory and writing appears from Latin through French to English. The Latin word *memoria* meant both "memory" and "memoir." In French, *la memoire* means "memory" and *le memoire* means "memoir." And English has the related words "memory" and "memoir," derived from French.

Throughout the centuries, a series of metaphors was proposed for mechanisms of memory, each in keeping with current practices and technology. Here are some examples: The metaphor of a dovecote or aviary was long used; we still refer to this when we speak of placing a memory in a mental pigeonhole.

In the Middle Ages, books as well as libraries provided metaphors of memory. In the nineteenth century, the rapid progress of technologies for recording and transmitting information provided a series of metaphors for memory. Photography (from the 1830s) was one; think of the expression "a photographic memory." Telegraphy, also from the 1830s, provided another metaphor. The telephone system, with its switchboard, offered a more flexible system in the 1870s. In 1877 came the phonograph, which provided a mechanical memory for sound. Early phonograph records inscribed the sound on wax-covered cylinders, thus updating the ancient technology of writing on wax tablets. Even in the late twentieth century, while research in the neurobiology of memory prospered, metaphors of memory based on recent technologies continued to be proposed, such as the digital computer and the hologram.

III. ADVANCES IN THE LAST QUARTER OF THE NINETEENTH CENTURY

By the last quarter of the nineteenth century, sufficient progress had been made in psychology and neurobiology for scientific research to begin in memory and its neural mechanisms. Psychology was becoming established as an independent academic discipline and as a laboratory science in Europe and North America. Wilhelm Wundt, a professor of philosophy with a doctorate in medicine, had founded the first formal laboratory of psychology at the University of Leipzig in 1879. William James, also a professor of philosophy with a medical degree, began teaching physiological psychology at Harvard University in 1875, and he had an informal laboratory of psychology.

The decade of the 1880s saw major advances in research on learning and memory. French psychologist Théodule Ribot published an important book, *The Diseases of Memory* (1881), in which he described and discussed impairments of memory as consequences of brain lesions and brain diseases. From his study of published reports, Ribot proposed that more recent memories were more likely to be impaired than were older memories. This formulation became known as "Ribot's law," and it was verified by experimental research a century later. In his book, Ribot wrote that he regretted that it was not possible to state impairments of memory in quantitative terms. Only a few years later, German psychologist Hermann Ebbinghaus showed how memory could be measured in his pathbreaking book *On Memory* (1885). This book inaugurated the experimental investigation of learning and memory, a field that soon expanded rapidly.

Contemporaries and immediate successors of Ebbinghaus soon enlarged the work he had started, emphasizing controlled research on memory in a laboratory setting. Although Ebbinghaus' research obviously encouraged others, they were ready to move in this direction, as was shown in a review by Postman:

> Ebbinghaus' paradigm did not dominate or constrain the development of the field in its early years. Not only were many new methods of measurement and types of materials introduced in rapid succession, but the kinds of questions that were asked about memory soon began to move in different directions (Postman, 1985, p. 127).

An important monograph on studies of verbal memory was published by Müller and Pilzecker in 1900. In it they put forth the *perseveration–consolidation hypothesis*, which engendered much further research. This hypothesis held that neural activity initiated by a learning trial continues and recurs for some time after the original stimulation has ceased and that this perseveration aids the consolidation of a stable memory trace. In reviewing this book, William McDougall (1901) pointed out that the perseveration–consolidation hypothesis could be used to account for retrograde amnesia following head injury.

A. William James (1890) on the Physical Basis of Habit and Memory

In his major textbook *Principles of Psychology* (1890), James devoted separate chapters to habit, association, and memory. James asserted that habit, memory, and other aspects of behavior are based on physiological properties of the brain, even when he could not specify those properties very clearly. Thus James stated that the cerebral hemispheres seem to be the chief seat of memory (p. 98). James devoted Chapter 4 to habit and Chapter 16 to memory; a related chapter, 14, was devoted to association. The separation of the chapters on habit and on memory can be seen as a precursor to the distinction made in the 1980s between nondeclarative and declarative memories. Habits, according to James, reflected the "plasticity of the organic material [of the nervous system]" (p. 105). Neural activity could either "deepen old paths or . . . make new ones" (p. 107). James admitted that it was not yet possible to define in a detailed way what happens in the nervous system when habits are formed or changed, but he was confident that scientific research would find the answers (1890, p. 107):

> [O]ur usual scientific custom of interpreting hidden molecular events after the analogy of visible massive ones enables us to frame easily an abstract and general scheme of processes which the physical changes in question *may* be like. And when once the possibility of *some* kind of mechanical[1] interpretation is established, Mechanical Science, in her present mood, will not hesitate to set her brand of ownership upon the matter, feeling sure that it is only a question of time when the exact mechanical explanation of the case shall be found out.

[1]James used *mechanical* here in the sense of mechanistic, that is, interpreting and explaining phenomena by referring to causally determined material forces.

James gave lessons on how to form habits effectively. And he drew an ethical lesson, with a molecular basis:

> Could the young but realize how soon they will become mere walking bundles of habits, they would give more heed to their conduct while in the plastic state. . . . Every smallest stroke of virtue or vice leaves its never-so-little scar. The drunken Rip Van Winkle, in Jefferson's play, excuses himself for every fresh dereliction by saying, "I won't count this time!" Well! he may not count it, and a kind Heaven may not count it; but it is being counted none the less. Down among his nerve cells and fibres the molecules are counting it, registering and storing it up to be used against him when the next temptation comes (1890, p. 127).

James distinguished between what later came to be called short-term and long-term memories, referring to them as "primary" and "secondary" memories (1890, p. 670). Concerning the tendency of emotionally exciting experiences to be remembered well, James wrote, "An impression may be so exciting emotionally as to almost leave a *scar* on the cerebral tissues" (1890, p. 670).

James devoted three pages (pp. 676–678) to the experiments of Ebbinghaus (1885) under the heading "Exact Measurements of Memory." Considering Ebbinghaus' curve of forgetting, James commented, "The nature of this result might have been anticipated, but hardly its numerical proportions" (p. 677). James praised Ebbinghaus especially for his novel and successful attempt to test experimentally between two opposed hypotheses: This referred to Ebbinghaus' evidence that serial learning involves not only direct associations between adjacent items but also the formation of remote associations between nonadjacent items. James commented that the fact of these remote associations

> ought to make us careful, when we speak of nervous "paths," to use the word in no restricted sense. They add one more fact to the set of facts which prove that association is subtler than consciousness, and that a nerve-process may, without producing consciousness, be effective in the same way in which consciousness would have seemed to be effective if it had been there (p. 678).

As of 1890 there were few techniques available to study neural processes that might occur during learning and memory formation or ways of studying possible effects of memory on brain anatomy or neurochemistry. The development and use of such techniques characterized the research of the twentieth century, but speculation about neural junctions as sites of change in learning were already prevalent in the late nineteenth century, as we note next.

B. Neural Junctions as Sites of Change in Learning

In the 1890s, several scientists speculated that changes at neural junctions might account for memory. This was anticipated, as Finger (1994) points out, by associationist philosopher Alexander Bain (1872), who suggested that memory formation involves growth of what we now call synaptic junctions: "For every act of memory, every exercise of bodily aptitude, every habit, recollection, train of ideas, there is a specific grouping or coordination of sensations and movements, by virtue of specific growths in the cell junctions" (p. 91).

Such speculations were put on a firmer basis when neuroanatomist Wilhelm von Waldeyer (Waldeyer-Hartz, 1891) enunciated the neuron doctrine, largely based on the research of Santiago Ramón y Cajal. Neurologist Eugenio Tanzi (1893) proposed the hypothesis that the plastic changes involved in learning probably take place at the junctions between neurons. He expressed confidence that investigators would soon be able to test by direct inspection the junctional changes he hypothesized to occur with development and training. About 80 years were to elapse, however, before the first results of this sort were announced.

Ramón y Cajal, apparently independent of Tanzi, went somewhat further in his Croonian lecture to the Royal Society of London (Cajal, 1894). He stated that the higher one looked in the vertebrate scale, the more the neural terminals and collaterals ramified. During development of the individual, neural branching increased, probably up to adulthood. And he held it likely that mental exercise also leads to greater growth of neural branches, as he stated with a colorful set of metaphors:

> The theory of free arborization of cellular branches capable of growing seems not only to be very probable but also most encouraging. A continuous preestablished network — a sort of system of telegraphic wires with no possibility for new stations or new lines — is something rigid and unmodifiable that clashes with our impression that the organ of thought is, within certain limits, malleable and perfectible by well-directed mental exercise, especially during the developmental period. If we are not worried about putting forth analogies, we could say that the cerebral cortex is like a garden planted with innumerable trees — the pyramidal cells — which, thanks to intelligent cultivation, can multiply their branches and sink their roots deeper, producing fruits and flowers of ever greater variety and quality (Cajal, 1894, pp. 467–468).

But Ramón y Cajal then considered an obvious objection to his hypothesis:

> You may well ask how the volume of the brain can remain constant if there is a greater branching and even formation of new terminals of the neurons. To meet this objection we may hypothesize either a reciprocal diminution of the cell bodies or a shrinkage of other areas of the brain whose function is not directly related to intelligence (p. 467).

We will return later to this assumption of constancy of brain volume and Ramón y Cajal's hypotheses to permit constancy in the face of increased neuronal ramification.

The neural junctions didn't have a specific name when Tanzi and Ramón y Cajal wrote early in the 1890s, but a few years later neurophysiologist Charles Sherrington (Foster and Sherrington, 1897) gave them the name *synapse*. Sherrington also stated that the synapse was likely to be strategic for learning, putting it in this picturesque way:

> Shut off from all opportunities of reproducing itself and adding to its number by mitosis or otherwise, the nerve cell directs its pent-up energy towards amplifying its connections with its fellows, in response to the events which stir it up. Hence, it is capable of an education unknown to other tissues. (p. 1117).

During the first half of the twentieth century, psychologists and other scientists proposed memory hypotheses involving either the growth of neural fibrils toward one another to narrow the synaptic gap or more subtle chemical changes at synapses (see review in Finger, 1994). But the techniques then available allowed little progress on this issue.

C. Introduction of Research on Learning in Animal Subjects

Research on learning and memory was extended to animal subjects independently by psychologist Edward L. Thorndike and physiologist Ivan P. Pavlov. Thorndike demonstrated in his doctoral thesis (1898), conducted under the supervision of William James, how learning and memory can be measured in animal subjects, using cats, dogs, and chicks. This research led to the concept of trial-and-error learning and, later, to the "law of effect" (Thorndike, 1911). The field Thorndike opened with this research was quickly entered by others (Hilgard and Marquis, 1940, p. 6).

In 1902, American psychologist Shepard I. Franz opened a further line in animal research on learning and memory. He sought to determine the site of learning in the brain by combining Thorndike's methods of training and testing animals with the technique of localized brain lesions. Franz later recruited Karl S. Lashley, and through Lashley many others, to research on this topic.

In contrast to Thorndike's planned study of animal learning, Pavlov came upon the concept of conditioning from observations on salivary responses, made during his Nobel Prize–winning research on secretions of the alimentary tract. His initial contribution to the study of learning has been dated anywhere from 1897 to 1904 or even 1906. The *American Psychologist* [1997, *52*(9)] and the *European Psychologist* [1997, *2*(3)] published parallel sections in 1997 to commemorate the centenary of Pavlov's book, in Russian, *Lectures on the Work of the Principal Digestive Glands* (Pavlov, 1897). Pavlov's book included observations on *psychic secretion*, which foreshadowed his later research on conditioning. The first published use of the term *conditioned reflex* (actually *conditional reflex*) was in a report by I.F. Tolotschinoff (Tolochinov), one of Pavlov's associates, at the Congress of Natural Sciences in Helsinki in 1902. Pavlov discussed conditioning in his Nobel Prize lecture in 1904, although the main subject of the lecture was the research on the digestive glands, for which the Nobel Prize was awarded. Pavlov's first paper in English on salivary conditioning was his 1906 Huxley lecture, "The scientific investigation of the psychical faculties or processes in the higher animals," which was published in both *The Lancet* and *Science*. Even this review did not, however, "lead to any immediate repetitions of Pavlov's work in America, so far as published records reveal" (Hilgard and Marquis, 1940, p. 10).

Conditioning is now such a widely used technique — including in the research reviewed in several chapters in this volume — that it is interesting to note that it did not gain acceptance rapidly. Only after the presidential address of John B. Watson to the American Psychological Association in 1915, "The place of the conditioned reflex in psychology" (Watson, 1916), did conditioning begin to gain a prominent place in textbooks, and its place in the laboratory lagged behind still further. The publication in 1927 and 1928 of translations of books by Pavlov, revealing the wealth of facts discovered by Pavlov and his colleagues during more than a quarter of a century of research on salivary conditioning in dogs, stimulated a series of replications and extensions to conditioning in other species.

1. Earlier Observations of "Psychical Secretion"

In evaluating Pavlov's contributions, it is important to note that Pavlov, as he stated in his 1904 Nobel Prize lecture, was not the first to observe that secretions of the salivary and gastric glands can be evoked by "psychic" (i.e., non-gustatory) stimuli. Although Pavlov did not feel it necessary to name his predecessors in this respect, several medical or physiological investigators recorded such observations in the eighteenth and nineteenth centuries, and many more must have seen this phenomenon. One of the earliest such reports I have seen is that of Robert Whytt in his book *An Essay on the Vital and Other Involuntary Motions of Animals* (1763, p. 280):

> We consider, that not only an irritation of the muscles of animals, or parts nearly connected with them, is followed by convulsive motions; but that the remembrance or *idea* of substances, formerly applied to different parts of the body, produces almost the same effect, as if these substances were really present. Thus the sight, or even the recalled *idea* of grateful food causes an uncommon flow of spittle into the mouth of a hungry person; and the seeing of a lemon cut produces the same effect in many people. . . . The sight of a medicine that has often provocked [sic] vomiting, nay, the very mention of its name, will in many delicate persons raise a nausea.

Note that in the last sentence, Whytt also anticipated Garcia's (1990) *bait-shyness* learning. Further descriptions of salivary responses presumably elicited by learned stimuli were made by Erasmus Darwin (the grandfather of Charles Darwin) in 1796, French physiologist C.-L. Dumas (1803), Claude Bernard

(1872), and others, as I have documented elsewhere (Rosenzweig, 1959, 1960).

Pavlov's contribution was not to discover this phenomenon but to investigate it. He was the first to demonstrate that salivation could be evoked by a previously neutral stimulus after this had been paired with an effective stimulus. And he investigated carefully and skillfully both the conditions under which such acquisition occurs and conditions that do not lead to acquisition even though stimuli have been paired. This is one of many instances in the history of the field in which a casual observation has been exploited to lead to an important advance in knowledge.

2. Pavlov's Physiological Theory

The fundamental concepts in Pavlov's physiological theory, as summarized by Hilgard and Marquis (1940), were excitation and inhibition, conceived as states or processes located in the cerebral cortex. Afferent stimulation by an originally neutral stimulus caused an excitatory process to be initiated at a particular point *A* on the cortex, from whence it spread or irradiated over the cortex. The irradiating excitation

> will be concentrated at any other focus of excitation, such as that aroused by an unconditioned stimulus. After a number of repetitions of the two stimuli, the excitation aroused by the neutral stimulus is drawn to the locus of the unconditioned stimulus in sufficient intensity to elicit the unconditioned response. The direction of the drainage of excitation is from the weaker to the stronger or more dominant focus of excitation (Hilgard and Marquis, 1940, p. 310).

These concepts were elaborated by Pavlov to account for such phenomena as conditioning, generalization, and extinction and also for sleep, hypnosis, and neurosis.

In spite of the tempting simplicity and scope of Pavlov's conception of cortical physiology, Hilgard and Marquis (1940) noted that it did not attract any wide degree of acceptance. Two of the primary objections they summarized are these:

1. Concepts of cortical physiology should be based on direct measures of cortical function, but Pavlov's "excitation" and "inhibition" were purely inferential concepts based on overt movements or amounts of saliva secreted (Hilgard and Marquis, 1940, p. 312).

2. Pavlov's physiological conceptions are explicitly based on the premise that conditioning is exclusively a cortical function. Recent experimentation . . . demonstrates, however, that conditioning is possible at a subcortical level. . . . The two-dimensional character of Pavlov's irradiation concept does not easily permit extension of the theory to embrace the integrated functioning of cortical and subcortical centers" (p. 313).