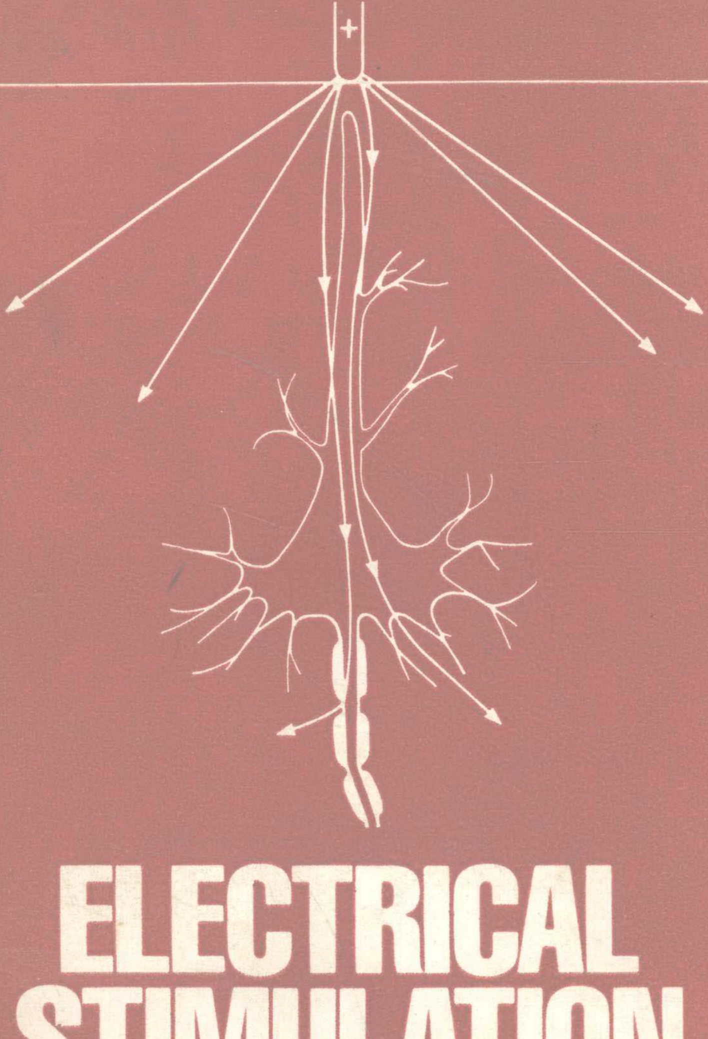
METHODS IN PHYSIOLOGICAL PSYCHOLOGY: VOLUME III



ELECTRICAL STIMULATION RESEARCH TECHNIQUES

Edited by

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Electrical Stimulation Research Techniques

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With a Foreword by Richard F. Thompson

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Foreword

The major approaches that characterize the organization and functions of the brain can be grouped into four broad categories of techniques: electrophysiology, anatomy, chemistry, and behavior. All of these approaches to the study of the brain and its functions will be treated in this series, Methods in Physiological Psychology. The series began with a three-volume work "Bioelectric Recording Techniques" (Thompson and Patterson, 1973) and continued with the volume "Neuroanatomical Research Techniques" (Robertson, 1978). The current volume appropriately treats the other side of electrophysiology: electrical stimulation.

Electrical stimulation of the brain has been perhaps the most widely used and abused technique in the study of brain and behavior. Historically, the first application of direct electrical stimulation of the brain, by Fritsch and Hitzig in 1870, localized the motor area of the cerebral cortex and led ultimately to an understanding of its fine-grained organization. Over the years, the method has led to a number of major discoveries, perhaps the most important being electrical self-stimulation of the brain by Olds and Milner.

Electrical stimulation of nervous tissue is easy to do but difficult to do well. Problems include tissue damage, current spread, and interpretations of stimulation effects. In this volume Dr. Patterson and Dr. Kesner have done an admirable job of bringing together a group of leading experts who have in turn contributed superb chapters on topics ranging from intracellular stimulation to electroconvulsive therapy. As with the previous volume of this series, the chapters are not merely descriptions of techniques, although they are, of course, outstanding in this regard. The chapters emphasize conceptual issues and convey considerable knowledge and wisdom about the fascinating field of the brain and behavior.

RICHARD F. THOMPSON

Preface

As early as 1780, Galvin stimulated frog nerve and observed the resultant muscle twitch. Since that time, electrical stimulation of various types has been widely used in physiological and psychological research. Early in its history, electrical stimulation was used at a gross level to define brain areas receiving primary sensory inputs and as the motivational tool in psychological studies. As both the understanding of electrical potentials and techniques of stimulus delivery improved, stimulation in the periphery and in the central nervous system became more intensively utilized in mapping neural circuitry as well as in motivational research. More recently, the complexities involved in stimulating neural populations have been more fully recognized and have led to a more cautious use of electrical brain stimulation (EBS) for reasons of both theory and technology. These problems are now being overcome, and as a result, electrical stimulation is more frequently being used as a tool for elucidating the mechanics of brain function.

Techniques with such a long and rich history are often shrouded in mystique and at the same time are often used indiscriminately. In the case of electrical stimulation, probably the latter has been predominant. The delivery and parametric features of electrical stimulation are often cavalierly ignored by researchers as they use a technique that seems both simple and direct. Such indiscriminate application of electrical energy, whether in the periphery or in the brain can often have confounding effects on desired results through such mechanisms as spread of excitation, interference with recording devices, or alterations in the physiology of the organism. In addition, the complicated physics of electrical energy interacting with neural systems is not to be taken lightly. If used properly, however, electrical stimulation has been proven to provide an extraordinarily useful and powerful technique for the elucidation of behavioral and neurophysiological mechanisms underlying psychological processes.

A number of books and isolated chapters have appeared over the years emphasizing the application of electrical stimulation in elucidating physiological function and behavior with moderate emphasis on theory, methods, and varieties of use. However, since Sheer's 1961 book "Electrical Stimulation of the Brain," no comprehensive work emphasizing theory, techniques, and applications of electrical stimulation has appeared. Given new technological developments and further understanding of the mechanism of the action of electrical stimulation, it is an appropriate time for a work that emphasizes these aspects. Thus, the present book brings together experts in their respective fields who use electrical stimulation techniques at various levels of the organism to elucidate numerous physiological and psychological processes. The book is organized from molecular uses of electrical stimulation in the brain to global applications in peripheral shock. Some of the theoretical and technical issues that are addressed have received attention for many years but have never been brought together in the unique ways utilized by the authors of this book. Each chapter presents not only the technological details necessary to utilize the technique being discussed, but also theoretical background as well as insights from the user's own experience. The richness of experience that has gone into each chapter will provide the reader with insights not available in any other format and should allow an enlightened use of various techniques by either the novice or the more experienced researcher.

The first part of the book (Chapters 1, 2, and 3) deals with stimulation at a cellular level. In Chapter 1, Ranck discusses stimulation at an extracellular level with emphasis on both the principles involved and the practical use of extracellular stimulation for examining various brain functions. In Chapter 2, Byrne deals with the problems involved in stimulating within a single cell in the central nervous system and presents many useful circuits and monitoring techniques for this very complicated procedure. In the third chapter, Asanuma details his techniques for microstimulation of small groups of neurons and presents lucidly the applications as well as limitations of this relatively new procedure. In Chapter 4 by Doty and Bartlett and Chapter 5 by Delgado, the authors treat the use of electrical stimulation in larger brain areas, both in animals and humans, and present considerable detail on the problems associated with electrical charge transfer in the medium of the brain. The next two chapters (by Gallistel, and Berman and Kesner) contain excellent discussions on the use of electrical stimulation in psychological research as a tool in motivation, reinforcement, and memory processes. In these chapters is presented some of the complexities underlying the interpretation of psychological studies in which electrical stimulation has been employed. In Chapter 8, Isaacson considers one of the more complicated enigmas of electrical stimulation by contrasting it with the effects of lesion work in which it is clear that lesion and stimulation are not always equal and opposite in effect. In the next chapter, Denney gives an excellent review of electrical convulsive therapy in humans and provides a lucid argument for its continued careful use. In the tenth chapter, Swett and Bourassa provide one of the more complete and authoritative accounts of the techniques and theoretical complexities of electrical stimulation of peripheral nerves that has ever appeared. This seemingly simple technique is one that has often been misunderstood, and their chapter provides much-needed information. In the last chapter, Masterson gives an account of the application of electrical stimulation through grid and peripheral means. This technique, often used indiscriminately, is discussed here in great detail and should provide a wide range of researchers with a lucid description on this valuable research tool.

As is evident from this overview, the chapters provide a comprehensive review and synthesis of most of the electrical stimulation techniques used today. The rapid growth of methodology and technology in these areas has allowed many of these techniques to enjoy more use in recent years. The authors must be commended for their enlightened and updated descriptions of both the positive and negative aspects of their techniques.

The book is written and organized for use by both the experienced investigator and the novice—for those with a detailed knowledge of physics and electrical interactions as well as those who are approaching the area with a very limited knowledge of these interactions. We would like to take this opportunity to thank the College of Osteopathic Medicine at Ohio University and the Department of Psychology at the University of Utah for their support, the authors for their diligence, and the staff at Academic Press for their patience and assistance.

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Chapter 1

Extracellular Stimulation

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I. Introduction

This chapter is intentionally pedagogic and simple. I have tried to discuss all of the known facts and principles of extracellular stimulation of the mammalian central nervous system, but I have tried to write it so that someone who is almost totally unfamiliar with the subject matter can follow it. Appendix I deals with current flow and should be read by those who do not know these physical principles as applied to excitable tissue. Appendix II is a simple statement of current flow in the brain. These facts and concepts are not widely known, and should be read by anyone unfamiliar with them. This chapter assumes the reader knows the facts and concepts in Appendixes I and II. Much of the research in this field involves mathematical or biophysical analysis; however, this chapter will not use mathematics, and the physical principles will be discussed in as simple terms as possible. The intent is *not* to instruct the reader on current research in the field, but rather to instruct the reader how to stimulate the brain with extracellular stimulation for uses in real experiments.

There is a major point that must always be remembered when talking about electrical stimulation of excitable tissue: *We stimulate cells*. It can be misleading to speak of stimulating a brain, a lateral hypothalamus, or a sciatic nerve. Whenever we have stimulating electrodes in a structure containing excitable cells and when enough current is passed, some cells that have parts in the vicinity of the stimulating electrode will be stimulated and others will not. Our ability to predict which cells will be stimulated is limited at present; however, we can predict it to some extent. The facts and the principles involved in this prediction will be developed in this chapter.

II. Basic Principles—The DC Case

An action potential is initiated by a depolarization of the transmembrane potential (V_m). The transmembrane potential (or voltage) is the difference between the voltage inside the cell (V_i) and the voltage outside the cell (V_o). Thus,

$$V_m = V_i - V_o.$$

Depolarization can thus occur by changing either V_i or V_o, or by changing both of them. When a microelectrode is put inside a cell and current is passed through the microelectrode, the cell will be depolarized by a current passing outward across the cell membranes. (In Appendix I the principles of current flow in tissue and across cell membranes is developed.) The greater the current crossing the cell membrane, the greater the depolarization. In this case, almost all the transmembrane voltage change is in the voltage inside the cell (V_i). The voltage outside the cell (V_o) changes very little, but this is not the case we are interested in.

When current is passed extracellularly, most of the voltage change is in the voltage outside the cell. We change transmembrane potential (V_m) primarily by changing the voltage outside the cell (V_o).

To explain what happens in real cases, it will be useful to first develop four extreme cases, all of which will involve stimulation by a monopolar cathode. The extracellular voltage due to this monopolar cathode will be most negative near the electrode tip and fall off with distance from the tip. Only the steady state (dc) case will be discussed initially.

CASE 1 (Fig. 1). The extracellular voltage (V_o) around a round small cell, say 20 μm in diameter, is made more negative by passing current. The ionic mechanisms working to maintain transmembrane potential (V_m) are unaffected, so the transmembrane voltage remains the same, and the voltage inside the cell (V_i) becomes more negative by the same amount as the extracellular voltage. The cell is *not* depolarized.

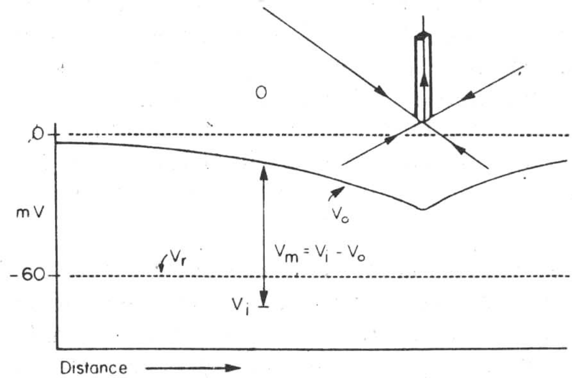

FIG. 1. A small diameter cell in an extracellular field (Case 1).
In Figs. 1–7, the abcissa is distance and the ordinate is voltage. V_o (extracellular potential), V_i (intracellular potential), V_m (transmembrane potential during current flow), and V_r (resting transmembrane potential, which is assumed to be −60 mV) are plotted as a function of distance. A stimulating monopolar cathode and lines of current flow (with arrows) are shown. The anode is a large distance away and is not shown.

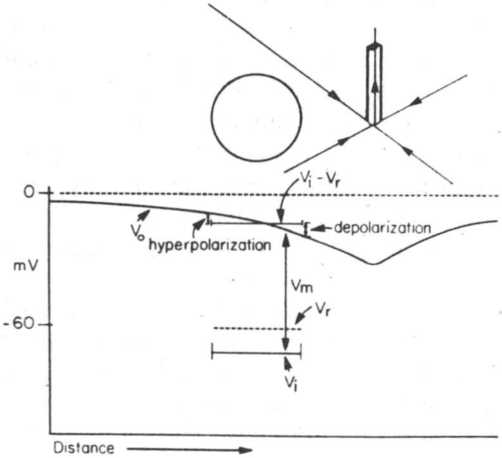

FIG. 2. A large-diameter cell in an extracellular field (Case 2).

CASE 2 (Fig. 2). A larger cell is in an extracellular potential field. Assume the membrane resistance of this cell is so great that no current effectively flows through the cell. Since there is no current flow in the cytoplasm, there can be no voltage difference in the cytoplasm, and V_i is the same throughout the cell. The ionic mechanisms maintaining V_m are the same, so the cell tries to maintain the same V_m. However, since the extracellular voltage (V_o) is not the same all around the cell, and V_i is the same everywhere, V_m cannot be the same everywhere. Roughly speaking, V_i will increase so that V_m is about the same on the average. This means that one side of the cell is depolarized, and the other hyperpolarized. Since we are interested in changes in V_m, it will be convenient to plot $V_i - V_r$, where V_r is the resting transmembrane potential.

CASE 3 (Fig. 3). This is the same as Case 2 except the cell is made to look more like a neuron. We are considering the extreme case of such a high membrane resistance that no current effectively flows through the cell. It also points out the fact that the larger the cell from end to end, the greater the maximum depolarization.

CASE 4 (Fig. 4a). Consider the case in which a neuronal membrane is of such low resistance that current flows freely across it. In this case, there will be current flowing in the cytoplasm of the neuron, and hence V_i will change with distance. For this very low resistance membrane,

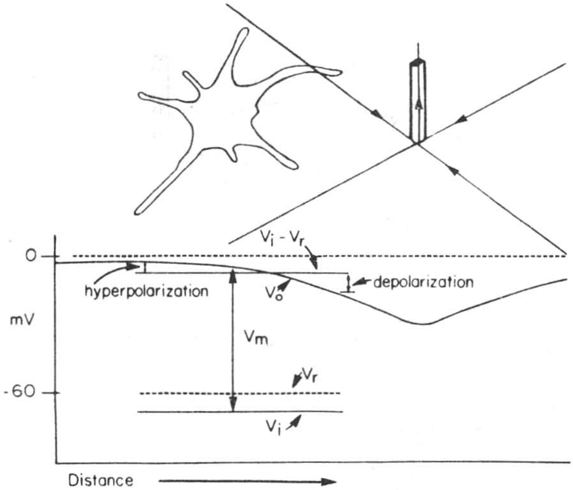

FIG. 3. Neuron with a very high membrane resistance in an extracellular field (Case 3).

changes in V_i will be the same as changes in V_o, and there will be no change in V_m anywhere and hence no depolarization. This never happens in the dc case but is approximately the case immediately after a pulse of current is turned on (see Section III-A).

CASE 5 (Fig. 4b) *The real case*, a cross between Cases 3 and 4. The membrane resistance of the neuron allows current to pass, but not freely. Current flows through the cytoplasm of the cell, so that there are changes in V_i with distance, but V_i does not change as much as V_o. One end of the cell is depolarized and the other hyperpolarized, but not as much as in Case 3. This leads to a result that may seem paradoxical to some. For the same sized cells in the *same extracellular* voltage field, the *more* current that flows through the cell, the less the depolarization. (If the current through the stimulating electrode increases, V_o will become more negative, more current will flow in the neuron, and it will be depolarized more. It is only in this sense that depolarization increases with increases in transmembrane current.)

Figure 5 gives the unrealistic case for a long fiber near a cathode, in which no current effectively flows through the cell. The depolarization is entirely due to V_o becoming more negative. This case is never true, but sometimes it is a fair approximation. Figure 6 gives the case where some current flows through the fiber, which is the real case.