ADVANCES IN PHYSIOLOGICAL SCIENCES

Volume 1

Regulatory Functions of the CNS Principles of Motion and Organization

Editors

J. SZENTÁGOTHAI
M. PALKOVITS
J. HÁMORI

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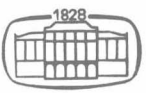

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FOREWORD

This volume is one of the series published by Akadémiai Kiadó, the Publishing House of the Hungarian Academy of Sciences in coedition with Pergamon Press, containing the proceedings of the symposia of the 28th International Congress of Physiology held in Budapest between 13 and 19 July, 1980. In view of the diversity of the material and the "taxonomic" difficulties encountered whenever an attempt is made to put the various subdisciplines and major themes of modern physiology into the semblance of some systematic order, the organizers of the Congress had to settle for 14 sections and for 127 symposia, with a considerable number of free communications presented either orally or as posters.

The Congress could boast of an unusually bright galaxy of top names among the invited lecturers and participants and, naturally, the ideal would have been to include all the invited lectures and symposia papers into the volumes. We are most grateful for all the material received and truly regret that a fraction of the manuscripts were not submitted in time. We were forced to set rigid deadlines, and top priority was given to speedy publication even at the price of sacrifices and compromises. It will be for the readers to judge whether or not such an editorial policy is justifiable, for we strongly believe that the value of congress proceedings declines proportionally with the gap between the time of the meeting and the date of publication. For the same reason, instead of giving exact transcriptions of the discussions, we had to rely on the introductions of the Symposia Chairmen who knew the material beforehand and on their concluding remarks summing up the highlights of the discussions.

Evidently, such publications cannot and should not be compared with papers that have gone through the ordinary scrupulous editorial process of the international periodicals with their strict reviewing policy and high rejection rates or suggestions for major changes. However, it may be refreshing to read these more spontaneous presentations written without having to watch the "shibboleths" of the scientific establishment.

September 1, 1980

J. Szentágothai

President of the
Hungarian Academy of Sciences

PREFACE

The first two volumes of the 1980 Budapest International Physiological Congress series were planned to contain the proceedings of the 11 symposia organized in Section 10, REGULATORY FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM. Although the symposia were in most cases unexpectedly well attended, and the lively discussions were limited only by the time factor, the number of manuscripts submitted varied considerably. From the symposia published in Volume 1 the participants of Nos 10/7 (chairman: K. Krnjevic), 10/8 (chairman: R. Baker), and 10/9 (chairman: L. M. Shik), and from Volume 2 the participants of Symposia Nos 10/2 (chairman: P. O. Bishop) and 10/3 (chairpersons: T. and P. Pasik) have to be complimented on their spontaneity and enterprising efforts.

In retrospect one cannot but have some misgivings about the way the various themes of the symposia had been selected and distributed among the sections dealing with different aspects of neural physiology. The work of the organizers of the section programmes was, of course, influenced by the availability and willingness of the prospective symposia chairmen. In addition, also the recommendations of the IUPS Council had to be taken into consideration while arranging the programme, to assure a fair rotation in the symposia subjects and chairmen to avoid having the same person presiding the discussions at successive congresses.

These difficulties were of minor importance compared with those inherent in the present status of the neurosciences. To secure stimulating interdisciplinary cross-communication between the various subdisciplines including neurochemistry, neuroanatomy, neurophysiology (from cellular biophysics to the global aspects of neural functions and to behavioural sciences), neuroembryology, neural genetics, molecular neurobiology, theoretical neurobiology, etc., societies and associations of the neurosciences have been born and have taken over the role of umbrella organizations. It was not easy, under these circumstances, to construct a coherent programme that would keep at least, to some extent, to the original disciplinary hierarchy of traditional physiology. We were probably somewhat overcautious in designing the programme of Section 10, the consequences of which became apparent, for example, in Symposium 10/5, where the omission of highly relevant anatomical information is regrettable in view of the original aim of the Symposium. Nevertheless, the Plenary Lecture published in Volume 1 may supply some of the lacking anatomical information.

These difficulties may account for the somewhat arbitrary division of the symposia proceedings of Section 10 into two books of which the first contains Motor Control as well as Organization Principles. The subtitle of Volume 2, Subsystems, has to be understood in the functional rather than in the structural sense.

If one were to look for general trends in the recent development of the neurosciences as reflected in these two volumes as well as in those of other sections dealing with neural mechanisms, one would find a sharp rise in the demand for studies on unequivocally defined neurons (or synapses on the finer scale). The injection of horseradish peroxidase (HRP) into axons and nerve cells, identified previously by the classical electrophysiological procedures, yields anatomical pictures that equal the best Golgi material, with a considerable gain in completeness of the dendritic and axonal arborizations within the range of a couple of millimetres. The high selectivity reached by staining single cells makes the recovery of electron microscopic section series relatively easy compared with the cumbersome technique to achieve the same on Golgi material. Even the finest details of synaptic contacts both given by axons and received by dendrites and cell bodies, and occasionally by initial axon segments, can be easily visualized. The corresponding (opposite) synaptic sites can, in turn, be identified by one of the appropriate anterograde (experimental degeneration, tritiated amino acid uptake) or retrograde (HRP) labelling techniques. Unfortunately, few of the papers presented exploited the potentialities of these techniques to this ultimate goal. The same possibilities of cross-identification are now available between physiologically and biochemically defined (as regards the synaptic mediators involved) neurons both by histochemical and immunocytochemical techniques. This approach can be further perfected to a complete physiological–anatomical–biochemical cross-identification down to the level of the electron microscope. Although the techniques are available, few of the reports made use of them more than in passing reference. Obviously, the authors were still more concerned with the main results of their general approach than with new refinements. In spite of the relatively low yield of specific results achieved with the new cross-identification techniques we believe that the trend of research in this direction is unmistakable and we are about to witness a dramatic development along these lines in the near future.

In pure neurophysiology there is a most impressive degree of sophistication in designing experiments. This approach–using a whole battery of stimulating electrodes to mimic natural stimuli, recording multiple electrodes or carefully predetermined tracks of several electrodes to record from closely neighbouring nerve cells, both extra- and intracellularly–has been around now for over fifteen years. However, the understanding of the function of definite portions of neural networks or of complex neuronal chains–not only under artificial but often under very natural behavioural circumstances–has reached an unprecedented depth. It is in this respect that the papers published in

these two volumes reach a standard where one is tempted to speak of a major breakthrough.

The general title of the Section REGULATORY FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM may not be so bad after all as it might appear at first impression when looking through the titles of the symposia and the list of papers. The leading pages in the symposia dealing with the various aspects of motor control and movement, especially eye movement, the cerebellum, the basal ganglia, as well as those concerning such overall functions like sleep, bear the characteristics mentioned in the preceding paragraph. It appears, hence, that neurophysiology has indeed reached a stage where the control aspects of neural functions can be successfully explored.

Budapest, August 1980

The Editors

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PRINCIPLES OF NEURAL ORGANIZATION

J. Szentágothai
1st Department of Anatomy, Semmelweis University Medical School, Budapest, Tűzoltó u. 58 H-1450, Hungary

My choice of title has set me something of a trap by seeming to imply that the problem/s/ of neural organization can be reduced to a few questions about the blueprints of neuronal connectivity, with very few functional considerations added. Since the principal question could be dealt with as well - or even better - within the conceptual framework of the molecular biologist, the cellular biophysicist, the biochemist, and of the ethologist - or more generally speaking of the behavioral scientist, I fear I may appear to be giving some ontological priority to one of the very different frameworks or levels of analysis at which the nervous system can be studied. Even worse, I might appear to be trying to reduce one of these frameworks into another, a danger which is now increasingly recognised /see for example MacKay - 1978, Rose - 1980/.

So what is the justification of my present approach? Simply this: It is my belief that in spite of my high regard for molecular biology, cellular biophysics, biochemistry, etc., these important disciplines, with all their sophisticated knowledge and technology apply to virtually all other organ systems and are not even confined to the animal kingdom. The very essence of the neural, separating it from all other living systems, is its unbelievably complex internal connectivity. In spite of chemical and other messages transmitted between various parts of the organ systems, and the complexity of the corresponding processing of information, nothing even remotely

similar is found in any other system of the living organism. In addition, I happen to be a neuroanatomist which would make it advisable - at least before such an audience - to stick to my own trade.

Neuroanatomy of today is characterised by an explosive development of techniques. To be sure, this is no longer pure anatomy, because it requires the combined approach of the most advanced microphysiology, biochemistry and immunocytology. We are now theoretically able - and in fact may demand this as a strict criterion - that any connexion or synapse studied, be identified both at the light- and the electron microscopic level as to its parent and receiving neurons, which must themselves be anatomically, physiologically, biochemically and immunocytochemically identified. I hope that I am not expected here to enter into the technicalities, which will be amply discussed at this congress. It will also be understood that we are at this stage very far from a synthesis, so that my modest attempts will be recognised as what they are meant to be: no more than the rudiments of - or perhaps some groundwork for - a synthesis that is yet to come.

The danger I see in the present situation - of this "embarras de richesse" - is that connectivity may be seen as some kind of magic tool destined to replace or at least swallow physiology and eventually to explain behaviour. Apart from the philosophical dangers I have hinted at, neuroanatomy - or more specifically neuron connectivity - has at the outset to come to grips with certain basic questions, often expressed as alternatives: neuron chains and reflex arcs versus neuron networks with central programs; or discrete pathways and centres versus distributed systems; or genetically preprogrammed connectivity versus plasticity, or even perhaps some randomness in connexions. Most neuroscientists will probably agree with my view that these concepts are not necessarily mutually exclusive, but rather different aspects of neural organization, all of which do represent some part of the truth.

Take for example the option of discrete pathways and centres versus distributed systems.

The application of modern retrograde labelling techniques, especially the uptake by nerve endings of HRP have shown us increasingly that we have greatly underestimated, even in the spinal cord, the length, variety, and distribution of intersegmental connexions to different target structures. This is more evident for the neurons of the upper part of the central core of the neuraxis, the lower brainstem - in which let me include, in a somewhat unorthodox manner, anything from hypothalamus and parts of the upper brainstem nuclei down to the medulla oblongata - where the ascending branches of the same neurons may extend as far up as the cerebral cortex and as far down as the spinal cord. This principle, demonstrated most elegantly by the Scheibels as early as 1958, may apply particularly to certain specific neuron types: the catecholaminergic or more generally the monoaminergic neuron systems. However, as shown also by recent studies in our laboratory on hypothalamic neurons, this applies also to regions lacking perikarya of these specific neuron systems, or containing only few local dopaminergic neurons. It would thus be unreasonable to deny the general validity of this principle for other neuron systems with more conventional kinds of synaptic mediators.

Already this sole example may convince us that the traditional view of ascending or descending chains of sequentially arranged neuron links cover at best one small part of the reality in overall neuronal connectivity. Since the longitudinally arranged and practically continuous neuron network of the entire neuraxis is connected everywhere, by both afferent and efferent connexions, with all the peripheral receptors and effectors as well as by ascending and descending ones with the higher integrative centers, we may hardly conceive of any two specific sites in any part of the nervous system that would not be interconnected by fewer than five neurons. A generalization like this, of course, is only an indication of an order of magnitude rather than an attempt at a realistic estimate. But

even so, we meet here the clear anatomic reality of a "distributed system" without having to abandon or even getting into conflict with the traditional concept of the "neuron chain". Both may easily be - and certainly are - valid at the same time.

I shall try to discuss the other apparently contradictory options relating to neuronal connectivity - particularly that of predetermined versus less determined addressing of connexions - while trying to answer a speculative question: What are some of the principles that might be useful in the assembly of such highly complex systems as those of the neural centres?

The building of a nervous system consisting of thirty billion neurons /3×10^{10}/ for the human brain* often with 10^{13} or 10^{14} synapses, is indeed a major feat of systems engineering, and difficult to envisage also in view of the relatively minute number of genes available /perhaps 10^{8}/. Do not think that I refer specifically to the human brain in order to overwhelm you by sheer numbers. Even the cat cerebellum contains 2.2 billion granule cells. This problem was most elegantly solved by nature by the simple trick of assembling the vertebrate nervous system out of "building blocks" of regular structure that could be used repetitively and would thus secure a relatively large number of quasi automatic connexions, thus radically reducing the number of specific genetic instructions required for a predetermined connectivity. This "building block" system applies equally from the macroscopic range down through the neuronal level to that of electron microscopic microanatomy. In fact, the electron microscopic structure of the neural centre looks rather reminiscent of an Escher drawing** with the difference that the fine structure of the

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* This rough estimate is based on the assumption of ten billion neurons in the cortex, close to as much for the granule cells of the cerebellar cortex and again ten billion for everything else.

** Maurits Cornelis Escher drawings containing interlacing irregular animal or human figurines.

neural centres is in three dimensions. I have often wondered whether this similarity could not be exploited to improve our understanding; but my romantic notions were cooled down soon enough by experts in discrete geometry who thought such an attempt - in three dimensions - out of touch with reality.

The "building block" principle is apparent already at the macroscopic level, its most generally known examples being the segmental organization of the neuraxis. But the most elegant and only relatively recently discovered cases are the assembly of the cerebellum, including both afferent and efferent connections in sagittally oriented relatively narrow discs, and the thalamo-cortical projection principle discovered by Kievit and Kuypers /1977/, according to which quasi-sagittal /slightly diverging/ slices of thalamic tissue project to coronal discs of the cerebral cortex. However, the real advantages of this architectural principle become apparent at the level of neuron assemblies - containing numbers of neurons of the order of tens to thousands - the so-called structural modules. The principle resembles that of the application of integrated circuits in electronics technology, when building blocks of various degrees of miniaturization secure proper connexions and interchangeability automatically by a certain repetitiveness in the regularities of outlets. Figure 1 shows the application of this principle to the central core of the spinal cord. In fact, the same principle holds for the lower brainstem - where it was first discovered by the Scheibels in 1958, although its full implications could not be realized at that time - and also, with certain modifications, even in the hypothalamus. As you may see, especially the central core - the intermediate gray matter - is built up of repetitive coin-shaped transverse discs, within which both the dendrites of cells and the entering axon terminals are rather strictly confined. The ventral and dorsal horns can be considered as appendages attached to this column of discs, which tend to penetrate into them so that each motor neuron belongs to a number of neighbouring discs with the appropriate interneuron connexions, although they have a number

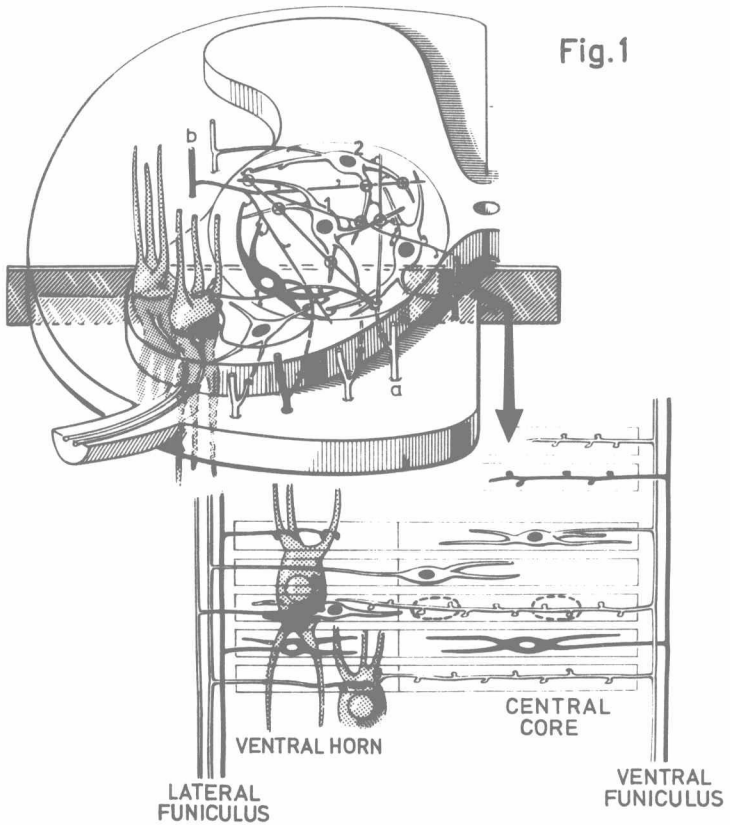

Fig. 1. "Stacked chips" architecture principle of the intermediate zone /centre core/ of the spinal cord, in the form of flat discs /represented as a circle in the upper transverse section diagram, and as brick-shape compartments in the lower longitudinal section diagram/. Assumed excitatory interneurons are indicated in outlines, inhibitory ones in full black; motoneurons are stippled. Note the straight courses of interneuron axon collaterals penetrating through the flat neuropil discs, by which they may establish synaptic contacts with any element encountered on their way. Certain potential contacts are considered "forbidden" by some "mismatch" between the respective elements /indicated by small circles, like - for example - between excitatory interneuron axon "a" and cell numbered 1 or inhibitory interneuron axon "b" with cell numbered 2. Further explanation in the text.