Nencki
Institute
of Experimental
Biology
Polish Academy
of Sciences

ACTA BIOLOGIAE EXPERIMENTALIS

Journal devoted to
basic research
in brain physiology
and
behavioral sciences

Vol. 29, No. 3/4, 1969

J. KONORSKI, editor
B. ŻERNICKI, associate editor

Lectures delivered at the scientific session held in commemoration of the 50th anniversary of the Nencki Institute
December 1968

Polish
Scientific
Publishers
Warsaw

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Acta Biol. Exp. 1969, 29: 229—237

Lecture delivered at the scientific session held in commemoration of the 50th anniversary of the Nencki Institute

December 1968

PROGRESS IN BRAIN PHYSIOLOGY IN THE PRESENT CENTURY

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In the present century and particularly since the end of the war in 1918 the rapid increase in scientific knowledge and in its applications has been one of the most striking features of modern civilisation. The advances have gone so far that in many lines of research it would be difficult now to recall what were the major problems that have been solved in these past 50 years, and difficult to remember how they were solved, and what were the problems which remain unsolved and have ceased to be interesting.

I shall try to review the progress which has been made in some of the fields of Brain Physiology particularly since 1918. This is the year when this Institute was founded and we shall hear from Professor Konorski about the particular kind of research on animal behaviour which has been followed here with such success. I shall be dealing mainly with research at a different level, not at that of behaviour and learning in the intact individual, but at the level of what we can find by looking at the organisation inside the skull, the detail of the central nervous system on which our behaviour depends, the fibres and tracts and networks and sheets of cortical substance, the cellular machinery which gives us the remarkable power not only of learning but of being aware of ourselves as intelligent individuals.

This is the aspect of the nervous system on which I used to lecture to medical students in Cambridge from 1918 to 1928 and at intervals later. I have looked at the notes of some of the lectures I gave, but I found them of little help. At that time most of them dealt with the gross ana-

tomical details of the nervous system or with the clinical evidence of motor or sensory disturbance in human subjects from injury or from disease.

But the Physiology of the Nervous System is one of the many branches of science which has to rely on technical improvements, and the course it has followed has often been set by the introduction of new apparatus or new ways of examining its material. So I shall deal in the main with some of the techniques which have led to the chief advances in our understanding of the brain.

In the modern era, the nineteenth and twentieth centuries, the first of all the important techniques which have helped us to study the central nervous system was that of microscopy. With the naked eye all we can see when we look at the brain or the cord is that parts of the substance are grey and parts are white. In the nineteenth century the microscope had shown the cells and the network of fibres in the grey matter, and the nerve fibres in the white, and in 1837 when Morse developed the telegraph system the standard picture of the central nervous system became that of the telegraph office with the nerve trunks as the cables to outlying places.

The staining and impregnating techniques which were used by Golgi and by Cajal were a great advance, for they showed the arrangement of cell body, dendrites and axon, and this led to a name which stood and still stands for a theory, but was accepted for its convenience, the name Neurone, invented by Waldeyer in 1891.

The theory, which had the support of Cajal, is that the nervous system is composed of separate Neurones, the cells with the long or short extensions which form the nerve trunks or the grey matter of the brain. The theory requires that the dendrites and axon of one neurone can make contact with those of another but are never fused with them. The networks which make up the grey matter are not continuous structures, they are made of the interlacing dendrites of separate units.

Now for twenty years after its birth, from 1890 to 1910, the Neurone theory was fiercely attacked by competent histologists who reported continuous fibrils of various kinds in the cells and networks of the grey matter. The contest was still undecided in 1908, when I started the medical course in Cambridge.

In 1906 however the Nobel Prize had been awarded jointly to Golgi and Cajal, the two great leaders in neuro-histology, and the lecture which Golgi delivered at the prize-giving in Stockholm is an excellent summary of fact and inference in the arguments for and against the neurone theory. He had begun by opposing it, and in 1906 he still considered the evidence for it not wholly convincing, but he was much less impressed by

the evidence brought by its main opponents, Nissl and Apathy and Bethe, and so he was inclined to agree with Cajal and accept it. By 1918 the Neurone Theory had come into general physiological thinking, though the controversy had had the valuable effect of drawing attention to the artefacts which could be produced in cells by the methods of staining in use. The methods which are now required for fixing and staining cells for the electron microscope are far more drastic, yet the results in the past few years have opened new chapters in neurohistology. The Neurone remains a single cell, yet we think of it now as a flourishing institution with various sub-departments of its own.

The microscope, whether optical or electronic, is needed to show us the cellular structure, but to learn the role of the various parts of the central nervous system we must have access to these parts in the living animal for stimulation or destruction or whatever procedures are involved in our experiments.

I do not think it is always realised how much easier experiments on the brain have become in the past half century: partly by special instruments and plastic materials like bakelite, perspex, etc., but mainly by new anaesthetics.

Until 1930 most of the experiments on animals which involved exposing the brain were carried out under anaesthesia by chloroform and ether. The laboratory staff would include experienced anaesthetists who could maintain a constant level throughout the experiment. There were few non-volatile anaesthetics in use, though urethane was sometimes employed for rabbits and chloralose for cats. With these there was not the same need for constant attention to avoid any fluctuation in the depth of anaesthesia, but the work of Sherrington and Leyton and of Graham Brown on cortical stimulation in the motor area of the primate brain was done with chloroform and ether.

In Great Britain and I believe in other countries it was not until 1930 that we began to use the Barbiturates. In the *Proceedings of the Physiological Society* for July 1930 there is a note which runs as follows:

The title is "Dial as an Anaesthetic for Surgical Operations on the Nervous System" by J. F. Fulton, E. G. T. Liddell and D. McK. Rioch (Oxford). It runs on as follows, though I have left out an occasional sentence:

"Dial Ciba" is a liquid preparation of diallyl barbituric acid possessing certain qualities which make it particularly valuable for experimentation on the nervous system. Even with profound degrees of anaesthesia spinal reflexes such as the knee-jerk remain active... With degrees of anaesthesia sufficient for operative procedures the motor cortex of monkeys continues to be electrically excitable...

The drug is especially valuable for observations on the responses of the motor cortex. In experimental surgery of the nervous system the drug has two important

advantages, viz. (1) it lowers blood pressure without material impairment of the heart's action or of respiration and it appears to constrict small vessels of cerebral vasculation with the result that major operations such as the removal of the cerebellum or cerebral hemispheres can be carried out almost bloodlessly without occlusion of any of the great arteries to the head.

This has made possible procedures involving exposure of the base of the brain which, owing to haemorrhage could be carried out under ether only with the greatest difficulty. (2) Animals remain quiescent for a period of 12 to 36 hours and this gives opportunity for satisfactory healing of the incision... Under this anaesthetic we have succeeded in performing three successive major operations on the same animal, such as removal at intervals of three weeks of the cerebellum, the right cerebral hemisphere and the left cerebral hemisphere and in monkeys it has been possible to extirpate bloodlessly one of the cerebellar hemispheres leaving the vermis intact.

I do not remember when Dial was joined by Nembutal and the other Barbiturates, but those with a rapid action, like Pentothal, were soon in use for the induction of anaesthesia in human patients. As far as experimental operations on the animal brain are concerned I am sure that few of the present lines of research described, for instance in recent numbers of the *Journal of Neurophysiology*, could ever have been followed in 1929 when Ether and Chloroform were still the chief anaesthetics.

In connection with operative procedure I ought to mention techniques developed by Sherrington for teaching and research. They are the techniques which enable us to examine the activity of some parts of the central nervous system reached by an operation, but not under the influence of an anaesthetic at the time of examination. The familiar example is that of the spinal or decerebrate cat which Sherrington used for his famous classes in mammalian physiology at Liverpool and then at Oxford in 1918 and onwards. The spinal preparation was made by decapitating the animal under chloroform and then giving artificial respiration. As soon as the effect of the anaesthetic had subsided the spinal reflexes would return and could be studied in isolation, without control by the postural centres in the brain stem.

The decerebrate cat was another preparation of the same kind, which he used to study the postural, brain stem reactions. The decerebrate preparation was made by a division at midbrain level (under chloroform) with destruction of the brain above it. Breathing would then continue and as soon as the effect of the anaesthetic had worn off the state of decerebrate rigidity, with increased extensor tonus, would develop. The decerebrate preparation, free from an anaesthetic, was the basis for most of the work of Sherrington and his pupils on the stretch reflex when he was at Oxford in the twenties.

I need not spend any time in an effort to trace all the far-reaching results which have come from Sherrington's work. It will be enough, I fancy,

to mention one or two of the now familiar words and phrases which have entered the physiological vocabulary because of the postural reflexes which Sherrington studied — Feed-Back, the "gamma loop", Cybernetics, and now Lateral Inhibition.

Another line of development of similar techniques was due to Bremer in the thirties. As before, the axis of the central nervous system was divided under an anaesthetic, which was then discontinued, but the object of Bremer's preparations was to examine the cerebral and not the spinal portion of the nervous system. He called them the *Cerveau Isolé* and the *Encephale Isolé* preparations and his experiments began an important new chapter in Brain physiology which is still being written. It is the chapter concerning the Reticular Formation — the collection of the neurones in the brain stem which are in touch with much of the sensory information which reaches the cortex and seems to control the general level of cortical activity and the changes from sleep to waking.

It has led to the work of Magoun and Moruzzi and Jung and others in research on sleeping and waking and on the physiology of vision.

But reverting now to instrumental techniques I should say that the development which has been of the greatest use to brain physiology is that of the electronic amplifier. This has made it far easier to record the electrical activity which occurs in the nervous system.

It has been known for over 100 years that activity in the peripheral nerves and muscles is accompanied by electrical changes, but sensitive and rapidly reacting instruments are needed to record them and in the central nervous system, where active elements are likely to be surrounded by inactive, the chance of short circuiting would be greater. Wedenski had detected electrical oscillations in the mammalian cortex by means of a telephone as early as 1884 and Gotch and Horsley had used the capillary electrometer in 1891 to record from the spinal cord.

These were insensitive instruments, but later in 1909 Einthoven at Leyden published the first descriptions of the 'String Galvanometer' which he had developed to give faithful records of the human electrocardiogram. He said that the instrument could be made far more sensitive than any mirror galvanometer and was also far more able to record very rapid electrical changes. The String Galvanometer, however, was an excellent instrument for recording the human electrocardiogram, the purpose for which it was designed, but it was not so well adapted for varied experimental work on other problems, for the 'string', the silvered quartz fibre which carried the current was extremely delicate and would break if it was overloaded.

It was used, none the less, for recording from the surface of the skull or the cortex, in dogs by Prawdzicz-Neminski in Kiev from 1912 to 1925,

and in man by Hans Berger in Jena from 1924. Both found waves with a characteristic frequency round about 10 a second. But to make such records the string galvanometer needed very careful adjustment, for the current variations which it had to record were close to the limit of its performance.

By 1918, however, the triode amplifier invented by Lee de Forrest in 1906 had been developed and used for wireless telephony. As Wedenski had found 40 years earlier, the electrical oscillations involved in the transmission of speech are not very different in frequency from those occurring in the nervous system, and several physiologists returned from their work in the war intending to use the triode amplifier (it had various names) to aid the recording of the electrical activity in living tissues, particularly, of course, in the nervous system.

In the physiological literature of the nineteen-twenties you will find several descriptions of circuits using the triode to amplify action-potentials of nerves, and in 1922 Gasser and Newcomer, at St. Louis, published the paper which really started the new epoch in electrophysiology by showing what great advances would be possible with this new technique. As many physiological laboratories by then had acquired the expensive string-galvanometer it was natural at first that this should be chosen for recording the amplified currents. For all but experts, however, the string was much too delicate to survive the occasional surge of current whenever the preparation or circuits needed adjustment. Some of the early attempts were failures for this reason and it was not until more robust recording systems were used that the value of electronic amplification for physiological work was generally seen.

As might be expected, the great increase in the possibilities of electrical recording brought other technical methods in its wake. One that we found exceedingly useful for detecting stray electrical interference as well as for presenting results to a large audience was the use of sound as well as of optical methods, for the output from the amplifier could drive a loud speaker as well as an oscillograph and the ear can recognise rhythms far more easily than the eye.

And another factor has come in to improve electronic apparatus for physiological research, for as soon as Berger's work was fully appreciated the human electroencephalogram acquired clinical importance and ink-writing oscillographs of many channels were needed in many hospitals. This has not reduced the cost, but has greatly reduced the time that used to be spent in physiological research if apparatus had to be assembled for simultaneous recording from several points in the nervous system.

There are two other more recent technical developments which ought to be mentioned. One is the use of microelectrodes able to lead from

a single axon or from the interior of a cell, and the other is the use of electrodes buried in the brain and left in place for stimulation or recording after the animal or the patient has recovered from the anaesthetic. And now with miniaturised equipment it is possible to stimulate or receive signals by radio transmission between the observer and the electrodes implanted in the subject's brain. Delgado has used this technique for studying rage reactions in primates and Brindley has stimulated many points in the human visual area in the hope of restoring some measure of sight to the blind.

I have dealt with these new techniques in brain physiology for they have transformed the subject in the past fifty years, and Ludwig was not far wrong when he said, 'In Science the method is all'. But the advances made by these methods are going in many directions and it is difficult to bring them together. I must try to select a few to show that we have not wasted our time.

There have, of course, been various false starts which have led to some waste of effort. Round about 1920, for instance, it was thought that the extensor tone in the decerebrate cat was maintained by the sympathetic system and it was several years before the idea was abandoned. It was also in 1920 that Lashley's *Studies of Cerebral Function in Learning* began to appear, and at the end of his life he was still 'in search of the Engram'. He had to confess that 'all he could find was where and what the memory trace is not'. But in spite of his failure to reach some positive answer I do not think anyone here would feel that Lashley had wasted his time. Though his problem remained unanswered his papers must still be read.

Again in the earlier days of electrical recording systems, before 1945, there were various attempts to trace the origin of potential waves in the cortex by making simultaneous records from several regions. Matthews and I spent much time and effort on such technically difficult experiments in 1934. It would certainly be far easier to make them now, but it cannot, I think, be said that even now we have reached any useful conception of the neuronal basis for most of the wave activity, the electrical oscillations which go on almost without ceasing in the human and animal brain. We can associate various rhythms, like those of the EEG (or their absence) with states of the nervous system, with sleep or dreaming, or attentive behaviour, and we find particular rhythms appearing in particular parts of the brain. They range from 10 a second in the cerebral cortex to over 100 in the cerebellum: they must be due to a number of elements acting in unison and they show no sign of the graded frequency, which we find in the sensory and motor neurones when they signal the state of the environment or order the muscular response.

Perhaps we have been too ambitious in expecting such simple expressions of activity as these wave rhythms to throw light on the complex problems of cerebral organisation, and perhaps we should be content to use them for medical diagnosis. At least they have drawn attention to one more circumscribed problem which puzzles us now — concerning the differences in cerebral activity in the states of sleeping and waking.

When the subject closes his eyes but remains awake, the α rhythm, the potential waves at 10 a second described by Berger, will appear in a large proportion of subjects (but not in all). If the subject then falls asleep the waves become intermittent and the α rhythm ceases or gives way to occasional groups with a slower and sometimes a faster rhythm.

It seemed natural that the brain would be less active in sleep, though it has now been found that there are periods during the night when rapid eye movements occur, when the electroencephalogram changes and the subject if woken will report that he has been dreaming. In this REM (rapid eye movement) period it is not surprising to find some new activity in the cerebral cortex, but now it appears that there is never a great reduction at any stage of sleep. In cats with microelectrodes implanted in the cortex the impulses recorded from single neurones may be differently grouped in sleeping and waking but there is no consistent reduction in the number discharged per second during periods of sleep. Like most unexpected findings this has the value of making us think again, in this case about the function as well as the cellular pattern of sleep.

But this unexpected result is a sign of progress. It has come because our technique has reached the stage when records can be made from single cortical neurones in animals unaffected by anaesthetics. And already this method has thrown fresh light on some of the problems of sensory orientation. One line of research relates to the way in which sensory information is analysed at different levels. Since 1959 Hubel and Wiesel have examined unit discharges in the visual cortex of cats and monkeys and have found that the neurones which react to a particular axis orientation of the visual stimuli are arranged in columns at right angles to the cortical surface and 0.5 mm or so in diameter. The same kind of columnar arrangement has been described for the somato-sensory cortex by Mountcastle.

Results of this kind have an added interest because of the evidence of contrast heightening by neuronal interaction, the lateral inhibition which Hartline has analysed in the Limulus eye and others have found in the vertebrate retina. We seem to be not very far from a general conception of the analysis of sensory information which takes us to the cortical level. At present we cannot go much further than the units in the receiving areas of the cortex, and new techniques may be needed

before we begin to understand how these afferent patterns of neuronal excitation and inhibition are brought to bear on the whole of the central organisation with its widespread rhythms and memory traces and power of directing behaviour.

Our technical progress has been more at the unit level than we should like, but it has scored some striking advances and we need not be too concerned if we have wasted some of our time.

Ludwig was not far wrong when he said — "In Science the method is all". But though we are grateful for all this technical progress, we cannot forget our leaders. Those of us here who remember Pavlov or Sherrington will be still more grateful for the inspiration which they gave, not only to us but to all who have studied the brain.

Acta Biol. Exp. 1969, 29: 239—249

Lecture delivered at the scientific session held in commemoration of the 50th anniversary of the Nencki Institute

December 1968

DEVELOPMENTAL PATHWAYS OF RESEARCH ON BRAIN-BEHAVIOR INTERRELATIONS IN ANIMALS

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It is quite natural that the celebration connected with an anniversary of a particular scientific institution induces us to look into the past and consider the development of the discipline which is represented by this institution. Of course, all reminiscences of this kind have a strong emotional character and this would certainly suffice for the speaker's undertaking the subject. I think, however, that besides the emotional aspect, such reminiscences are useful because the history of scientific ideas is undoubtedly important in properly evaluating the actual state of science, just as the developmental history of organisms is necessary for understanding their present state. I assert that these reminiscences are particularly important when they are based on the direct experience of the speaker and not on his second-hand knowledge based on a reading of old publications. Consequently, I consider the scientists of older generations to be particularly suitable for these reminiscences because the events which occurred in their disciplines 30 or 40 years ago are for them not bygone but reality, sometimes even more vivid than the present reality. Because I began work on the physiology of higher nervous activity exactly 40 years ago — my first paper with Stefan Miller was published in 1928 in *Comptes Rendus de Societé de Biologie* — I would like to devote my present talk to the events which occurred during these 40 years.

However, before I turn to my proper subject, I would like to dwell

for a while on the earlier period which is as prehistoric for me as for you the early thirities: I would like to consider the situation at the turn of our century in the discipline to be discussed.

Now, when the problem of brain-behavior interrelations has become both interesting and fashionable, many people of the younger generation think that studies on this problem originated in the second half of our century. This is, however, very far from the truth. In fact, first studies in the field of the modern physiology of the brain, initiated by the pioneer work of Flourens, Hitzig and Fritsch, Golz, Ferrier and others, consisted in ablations of various areas of the cerebral cortex in animals and in observations of how the animals behaved after these operations. In this way, attempts were made to learn the functional significance of a given cortical area. Thus, in the very beginning of research on brain activity, this organ was a priori regarded as a system serving to control animal behavior. The task of the investigators was to understand in which way this control is executed. These investigations became a foundation of our knowledge on brain activity, a foundation on which all later research was to be based.

It should be stressed at once that the chief drawback of these investigations was that at that time the specialized experimental methods in the field of animal behavior and learning, such as mazes, discrimination boxes, and above all, the methods based on conditioning, were very poorly developed and failed to penetrate into physiological circles. Therefore, these scientists were fully satisfied with the *general* observation of brain lesioned animals and with their neurological examination. Only a few authors, among them the Russian physiologists Pavlov and Bechterev (and their collaborators), the German psychologist Kalischer and the American psychologist Franz, began to apply behavioral tests to the study of animals with brain lesions.

After this short "prehistoric" introduction with regard to my own past we can turn immediately to the early thirties, that is to the period when I began to work on the problems of the brain-behavior interrelation. At that time experimental work on the acquired behavior of animals was developing at full speed, that is, work on conditioned reflexes in Pavlov's terminology, or habits, according to American students. Therefore, an urgent need emerged to create a theoretical basis, or to be more exact, a framework, in which the rapidly accumulated experimental data might be organized. And just at this point there arose acute controversies whose traces we can still observe or even feel at present. Also at that time extensive studies were published which depicted and synthesized the achievements and theoretical attitudes of particular scientists and their co-workers. These studies have played a most important role in the fur-

ther development of the discipline with which we are concerned. In particular I have in mind the following works:

1. *Conditioned reflexes, an investigation of the physiological activity of the cerebral cortex,* by I. P. Pavlov, a book which appeared in 1927 and was immediately translated into English, French and German.

2. *Individually acquired activity of the central nervous system,* I. S. Beritov's book which was published in 1932.

3. *Brain mechanisms and intelligence,* a monograph by K. S. Lashley, published in 1929.

4. *Purposive behavior in animals and man,* a book by E. C. Tolman, published in 1932.

5. *Principles of behavior,* by C. L. Hull, a book which appeared only in 1943, though the views of the author were known earlier from his previous publications.

6. *The behavior of organisms,* by B. F. Skinner, published in 1938.

I will begin my survey of the scientific attitudes concerning animal behavior with Pavlov. It is worth mentioning here for those who may not realize it that when Pavlov was starting, at the beginning of our century, his research on the physiology of the brain, he was already a world renowned scientist who had laid the foundations for the modern physiology of the digestive glands, work for which he won the Nobel Prize in 1904. While studying the secretion of salivary glands in dogs Pavlov came upon the phenomenon of the so-called psychic secretion which occurs in humans as well as in dogs; it consists in the occurrence of salivation not only when food is in the mouth but also when a subject sees the food, sniffs it and so on. Pavlov regarded psychic salivation as a physiological phenomenon, basically the same as purely reflex salivation; therefore, he referred to it as a conditioned reflex. According to Pavlov, the only difference between the conditioned reflex and the inborn or unconditioned reflex was that the conditioned reflex is more complex, that it is acquired according to an animal's experiences and that it depends on the higher centers of the nervous system. Pavlov clearly understood that the salivary conditioned reflex may be regarded as a convenient *model* for the acquired activity of the animal, of the activity controlled by the brain and particularly by the cerebral cortex. Just as on the basis of the course of spinal reflexes we may draw conclusions about the properties of spinal centers, so on the basis of salivary conditioned reflexes we may learn about the properties of the cerebral centers. To put it in modern language, one can say that from knowing the input signals of a given complicated steering design — in this case conditioned stimuli — and its output signals — in this case salivation — we can make conclusions concerning the internal structure of this design. In this way,

the tremendous research work of Pavlov and his many co-workers initiated the field which he called the physiology of higher nervous activity. It is highly significant that till the end of his life Pavlov remained faithful to the salivary glandular reflex as the indicator of the nervous processes he investigated. For, on the one hand, this approach made an excellent *quantitative* method of animal responses and on the other hand, he was thus able to avoid the immense complication and variety of phenomena involved in the motor behavior of animals. Pavlov was fully aware that the laws governing salivary conditioned reflexes apply to all other conditioned reflexes connected with other activities of the organism, a fact which was confirmed in further studies.

It is worthwhile to draw your attention to the interesting circumstance that Pavlov, in the first decade of his work on conditioned reflexes, continued to follow the old tradition of using the ablation method to study the brain. Thus, after the formation of certain conditioned reflexes in dogs, some parts of the cerebral cortex were removed and the disorders in these reflexes were examined. From this procedure, conclusions might be reached as to the functional significance of a given cortical area. However, in the following years Pavlov totally abandoned this line of research and devoted himself completely to the study of conditioned reflexes in dogs in which the only surgery done was providing the fistula of the duct of one of the salivary glands in order to measure conditioned and unconditioned salivation. This change of the line of research occurred because the study of conditioned reflexes established to various stimuli and their manifold combinations provided so much information about brain activity that the methods of cerebral lesions seemed to Pavlov superfluous. In other words, Pavlov adhered to a wise principle, formulated by Von Holst forty years later to the effect that brain research at its present stage of development should be concerned with the questions of "how" and "why" rather than with the question "where". And Pavlov tried to answer the questions of "how" and "why" precisely by changing and combining the signals entering the steering system and recording the only output signal he utilized, namely salivary secretion.

In Russia, or rather in Georgia, in the second decade of our century there arose another scientific center whose work to a great extent followed the line of Pavlov's research. This center was created by I. S. Beritov. His experimental method was basically the same as that of Pavlov, except that his indicator of cortical activity was not the alimentary conditioned reflex manifested by salivation, but the defensive conditioned reflex manifested by leg flexion to a conditioned stimulus signalling the stimulation of the paw by electric shock. From the very beginning of

his work in the field of conditioned reflexes (which he called "individual reflexes" in contradistinction to "species reflexes") Beritov was a vehement opponent of Pavlov.

Although Beritov did not questioned the experimental data obtained in Pavlov's laboratories, he denied the soundness of Pavlov's conclusions concerning the mechanism of the steering system, a mechanism which was the purpose of both these scientists' search.

It is not difficult to find the genesis of this controversy. Whereas Pavlov came to his study of the physiology of the brain from a very remote field of research — the physiology of digestion, Beritov was always a pure neurophysiologist and he tended to reconcile the principles of brain activity with those established for lower levels of the nervous system.

Since I am taking the role of a chronicler in these reminiscences I do not intend to enter into the details of this dispute or to evaluate who was right and who was wrong. I wish only to note that, as it follows from my previous considerations, the argument between the two scientists, or rather Beritov's attacks on Pavlov's theory, had a purely matter of fact character, since the principal attitude of both was identical: both attempted to discover the principles of brain activity on the basis of its input and output.

Now I will turn to a discussion of another opponent of Pavlov whose standpoint was much more at variance with him, and whose views influenced to a great extent the formation of scientific attitudes of the students of the discipline. I have in mind the American scientist K. S. Lashley, the author of a great number of experimental papers and the famous book *Brain mechanisms and intelligence.*

For the better information of the audience I would briefly like to present one of the most important series of experiments conducted by Lashley and conclusions he drew from them.

Lashley performed experiments on rats and trained them to run mazes of various complexities. He compared the rate of learning in normal rats with those having cerebral lesions of different sizes and locations. The results of these experiments were rather unexpected. First, it was found that the larger the part of the cerebral cortex removed, the slower the animal's mastering of the maze habit. Secondly, it was found that impairment of learning did not depend on the localization of the sustained lesion. From these experiments Lashley drew the following two conclusions: first, that the amount of the remaining cortical tissue determines the learning ability — a principle which Lashley called the law of mass action; and second, that various parts of the brain are in

this respect equivalent — a principle he called the equipotentiality of the brain.

I do not intend to describe other experiments of Lashley here, among others those which partially weakened the above thesis; my purpose is to emphasize the principal idea of his research, an idea which he held till the end of his life. This idea may be formulated as follows: no place in the brain exists where memory traces, or engrams, are maintained because as a matter of fact they are everywhere and nowhere; in consequence, any connectionistic conception of learning and conditioning is *a priori* doomed to failure. Hence Lashley denied the concept of the conditioned reflex as an elementary phenomenon of brain activity, based on a connection between the center of the conditioned stimulus and the center of the unconditioned stimulus.

It is most interesting to compare the scientific attitudes of Pavlov and Lashley. With regard to their *experimental* methods, Pavlov worked on dogs studying their salivary conditioned reflexes; Lashley worked mainly on rats by means of the maze method and the discrimination box of his invention. However, the more important difference is that whereas Pavlov as we have seen quickly abandoned cerebral surgery, insisting on answering the questions of "how" and "why", Lashley was concerned for his whole life with the problem of "where" and tended to answer this question by studying the effects of lesions of various parts of the cerebral cortex on the performance of specific tasks. Finally, whereas Pavlov was, in a manner of speaking, a "positivist" in science, that is he tried in every way possible to *understand* the phenomena he investigated by putting forward one hypothesis after another without fear of mistakes, Lashley was a typical "spirit of negation" and his chief purpose was to show: "you are wrong, your explanations are false". He was *sui generis* a devil's advocate in science, and not at all in the pejorative sence of the term.

Though I am not in the least abandoning my role of a chronicler I must state that Lashley's criticism of Pavlov's theory was not quite just and was based to a large extent on misunderstanding. For Pavlov was not only a great scientist but a very wise man as well, and he perfectly realized the immense complexity of the problem of brain activity. Furthermore, results were obtained in his laboratories which were similar to those discovered by Lashley — after the ablation of the visual area of the cerebral cortex differentiation of light intensity was unimpaired, and after ablation of the auditory area the differentiation of tones was preserved. Pavlov himself created the concept of "mechanical immunity" of cerebral tissue, a principle now called the infallibility of steering systems. On the other hand, Lashley fell into cognitive nihilism

too soon, he gave up too quickly as far as a positive explanation of his facts was concerned; for instance, he did not consider the possibility of the existence of *parallel* nervous pathways on different levels of the nervous axis, pathways which could replace each other in case of destruction of one of them.

In spite of all these reservations and discussions resulting from the immense complexity and, I would say, mystery of the steering system which is the brain of higher animals, Lashley held to the physiological standpoint consistently; he only insisted on that we cannot explain through connectionistic concepts where memory traces are laid down, and he maintained that the principles of brain activity are rather different from those which we usually imagine.

However, the scientific attitude of the group of scientists to whom I now turn is quite different. I have in mind Hull, Tolman and Skinner. And here again I must give a short "prehistoric" introduction.

The American psychologist Thorndike is generally considered the father of American (and even world) animal psychology based on experimental methods. The scientific attitude of Thorndike was very near to that of Pavlov — he claimed that the study of animal behavior should be purely objective and should not resort to introspective explanations. And Thorndike did not avoid attempting physiological explanations of the facts he obtained. Then, in the second decade of our century Watson, the famous American psychologist appeared on the scene; he regarded the objective approach to the study of both animal and human behavior as his main methodological program, and he has advanced a new scientific doctrine called by him "behaviorism", a doctrine which played an enormous role in the further development of behavioral sciences. It should be noted that at that time the news of Pavlov's early investigations of conditioned reflexes reached America and Watson accepted them enthusiastically, recognizing Pavlov as a chief prophet of behaviorism. Thus, in the thirties, the period in which we are interested here, behaviorism was already a widespread and generally acknowledged scientific doctrine.

And now something quite unexpected happened which is somewhat difficult to explain. Students appeared who, holding the objectivistic position in behaviorism and dismissing the subjectivistic treatment of animal behavior as unscientific, fought with equal energy against the *physiological* treatment of behavior. As a result there arose a large scientific discipline which deprecated both subjectivistic psychology and physiological approach to the study of behavior.

This historical event which we witnessed is all the more strange since the tendency to physiologize arose rather early in psychology, even before Pavlov, and was widespread at the end of the nineteenth and

beginning of the twentieth century. We should remember that the German psychologist Wundt, at the end of the nineteenth century, proposed the term "physiological psychology" he used as the title of his three volume treatise which played such an important role in psychology's development. In other words, the alliance between brain physiology and psychology was something rather natural and its strengthening was to be expected with the development of the physiology of the brain. Therefore, the break in this alliance committed by behaviorists in the thirties was quite unexpected.

Since I am not a behaviorist and I was not a direct witness to this break I cannot offer reasons for it. The eminent Canadian psychologist D. O. Hebb, who belongs to the physiologizing group of psychologists, asserts that the blame for this process should be placed precisely on Lashley whose nihilistic attitude toward all theories of physiological explanations of animal behavior and whose continuous propagation of the position of "ignoramus" was responsible for the credibility gap in physiology as a discipline from which psychologists could expect assistance.

Let us see what offer was made by behaviorists in exchange for the subjectivistic attitude they abandoned and the physiological attitude they rejected. Here two lines of thought may be discerned. One line of thought is represented by Hull, Tolman and many of their followers. These scientists professed various *formalistic systems*, involving "intervening variables" put between stimuli and reactions, and accounting for their interrelations. The difference between this approach and that of a physiologist is quite essential. If a physiologist puts forward hypotheses concerning the mechanisms of the brain, he *must* take into account, and make use of the *general principles* of the functioning of the nervous system. On the other hand, for a behaviorist such limitations do not exist, since his "constructs" linking the stimuli with the reactions are purely formalistic and devoid of any actual content.

What was the attitude of Hull and his followers to the achievements of Pavlov's school? It was most positive as far as their behavioral aspects were concerned. Hull utilized the experimental results of the Pavlovian school to a great extent and he included these results into his formalistic system. Accordingly Hull's doctrine is often referred to as the neo-Pavlovian doctrine.

Here for example is a curiosity of Hull's thinking. In his system the quantitative relations between the stimulus and the response play an important role and, following Pavlov, he introduces intervening variables representing both excitation and inhibition. Hull proposes the *units* of these variables and denotes the unit of excitation as "Wat" from the

name Watson and the unit of inhibition as "Pav" from the name Pavlov. Consequently a given response may be the result of so many Wats minus so many Pavs.

I will now turn to considering another principal personality in behaviorism, in whose hands this doctrine became even more radical or positivistic than with Hull, that is to Skinner. Skinner created an experimental method consisting in that the animal performs a definite simple movement — a rat presses a small lever and a pigeon pecks a small window — under alimentary motivation. Thus, in principle this method is the same as the method of Type II conditioning introduced by Miller and me. However, the utilization of this method in Skinner's experiments is quite different. Skinner introduced various "schedules of reinforcement": in fact one can reward the animal for every lever press (or peck), or for each definite number of presses, or one can reward only those presses which follow one another with a given frequency, and so on; since the schedules of reinforcement are programmed beforehand and fully automatized, the animal is left to itself for hours and even days.

Now Skinner is neither interested in the physiological mechanisms controlling the animal's activity nor even, so to speak, in imaginary mechanisms provided by Hull and others. He is interested only in the purely empirical level of the phenomena concerned and does not go beyond this level. In spite of the fact that such an approach may seem to many people completely sterile, it won a great many followers, and the "Skinner box" is one of the most popular behavioristic methods. For Skinner the ideal theoretical model of his approach was Newtonian mechanics, and Newton's famous statement "hypoteses non fingo" was the leading idea of scientific conduct for Skinner. This being so, there is no wonder that Skinnerians form a sort of isolated group, or rather sect, possessing their own journal with the significant title: *The Journal of Experimental Analysis of Behavior*. The group has its own very sophisticated problems in trying to discover which refined schedules the animal is able to master.

The above somewhat pejorative description of Skinnerism is not quite fair because some investigations based on the Skinnerian method can be utilized in problems going far beyond the field of pure empiricism and have great significance in the field of brain physiology and brain pharmacology. Consequently one may note an interesting difference between the *intentions* of a scientist when he invents a new method and an ultimate *use* of that method. The method of conditioned reflexes was invented by Pavlov for the study of brain activity, but it has played a tremendous role in behavioristic psychology which repudiates the physiological approach to the phenomena in question. In contrast, the Skinner method, which was invented for the creation of a purely positivistic

and empirical system of behavioral science, is a valuable instrument for the study of brain-behavior interrelations.

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Such were the discussions and controversies in the fourth decade of our century, just before the terrible and tragic cataclysm of the Second World War. However, as is seen from the history which we experienced ourselves, even the most terrible cataclysms can only *disturb* the progress of science, just as logs thrown into a river can disturb its course, but cannot *inhibit* it. Therefore, after the War the course of investigations continued and the old discussions and controversies have revived. Because of the rapidly running time of this lecture I am not able to trace the further development of the scientific events which were described here, and so I shall jump directly to the year 1968 to see how those *dramatis personae* whose ideas I presented above look like now.

Let us begin again with Pavlov. Pavlov died in 1936. There was a time when the significance of his achievements seemed to decrease, but soon there was a new turn of events. For, with the improvement of methods of brain physiology, and particularly, as experimental neurosurgery reached a high technical level, when it became possible to perform precise operations on the brain taking into account its anatomical organization, when it became possible to implant electrodes into definite places in the brain and stimulate these places in waking animals, and, finally, when it became possible to record action potentials from neuronal groups or even single neurons in these animals, then at last, thirty years after Pavlov's death, his dreams were fulfilled. The physiology of the brain as a system steering animal behavior received a strong developmental impulse because it became possible to look into this system and directly observe its activity. And then the method of conditioned reflexes — those simplest and best understood responses controlled by the brain — immensely gained in significance. Therefore, in more and more laboratories devoted to the study of brain physiology, the conditioned reflex methods in their various forms found their proper place.

Concerning the main opponent of Pavlov, I. S. Beritov, he continues with great vigor to pursue the line of investigation he began about 50 years ago, broadening the scope of research and deepening his physiological concepts on the mechanisms of the brain function.

In connection with an enormous development of the physiology of higher nervous activity, or physiological psychology, or neuropsychology, or physiology of the integrative activity of the brain — this last term seems most suitable to me — this scientific discipline overtakes the positions previously occupied by behaviorism. For, one cannot continue to

treat the animal's skull as a black box about whose interior one can know nothing, at a time when one is able to look into this interior by means of electrodes recording action potentials, to remove bits of this interior by neurosurgical operations, or to influence directly this interior by electric stimulation or psychotropic drugs.

If we depict the present state of behavioral sciences in the general terms, its most accurate characteristic seems to be the following: All the investigations connected with the direct manipulation of the animal's brain, including the vast repertory of behavioristic methods, were assimilated by physiology. On the other hand, investigations concerning various forms of acquired animal behavior carried out by the pure input-output methods without intruding into the brain itself are now polarized: either they preserve the character of formalistic behaviorism, or they approach physiology more and more.

To end, a few words about Lashley. Lashley died in 1958. The edge of his nihilistic theoretical attitude discussed earlier seems to have become less sharp, simply because as we better and better understand the principles of the activity of great nerve nets, the problems which seemed unsolvable in Lashley's time do not look so hopeless now. And although we are still very far from their solution, we at least see the beginning of paths which we can enter. Furthermore, it should be remembered that Lashley was one of the main pioneers of the application of ablation methods to behavioral sciences, and his research work in the field of visual perception in rats, the work which showed that, after all, the cerebral cortex is not so anonymous and equipotential as he propagated, has played a very important role in physiological psychology.

It can be seen from this epilogue that at the end of his narration the chronicler suffered a breakdown in his objectivism and gave opinions about the values of our distinguished precursors, opinions with which one can agree or not.

But this is the fate of the majority of chroniclers and perhaps it is not so bad. For if a narration about the past can serve to pave the way for future research, we cannot avoid giving such opinions, because our decisions about the further development of our scientific discipline depends on how we evaluate various aspects of the past. The only important thing is to clearly separate the field of facts from the field of their evaluation; for, the history which I have just presented shows how much these evaluations can change in the course of years, while the factual data, if they are correct, remain the same.

Acta Biol. Exp. 1969, 29: 251—269

Lecture delivered at the scientific session held in commemoration of the 50th anniversary of the Nencki Institute

December 1968

THE SIGNIFICANCE OF VOCAL IMITATION IN ANIMALS WITH SPECIAL REFERENCE TO BIRDS [1]

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The vocalizations of birds are, of course, to be regarded as essentially a form of "language"; a communication system which conveys information of various kinds between the mates or potential mates of the species, between members of a family, between members of an organised flock, and to some extent between different species. It is often convenient to divide these vocalizations into two types: (i) song — which is a type of vocalization appropriate to, and often confined to the breeding season, given primarily by the male, under the general physiological control of the sex hormones, and often capable of a high degree of modification by imitative learning. (ii) Call-notes, on the other hand, are usually much simpler in structure, consist of one or a few bursts of sound in contrast to the longer and more complicated sequences of the song, and in the main, convey information which may warn of danger, help to control the movement of the flock and so forth. However, though these two types of vocalization do merge one into the other, today I shall be discussing primarily the first and shall not have very much to say about call-notes.

The essential problems which birds have to face as social animals if they are to make effective use of their vocal and auditory mechanisms for communication, can be briefly set forth as follows:

I a. To produce and maintain *species distinctiveness* of vocal signals.
b. To produce and maintain *group distinctiveness* of vocal signals.
c. To produce and maintain *individual distinctiveness* of vocal signals.

[1] Dedicated with affection and respect to Professor Theodosius Dobzhansky on the occasion of his 70th birthday.

II. To recognise the signals and produce the correct responses in each case.

First in regard to the mechanisms which we must assume to be operating if these conditions are to be met, let us consider under I(a) above, the question of securing and maintaining *species distinctiveness*. Here we have to establish the mechanisms for the maintenance of the overall specific pattern of song from generation to generation. How much of this can be put down purely to genetic programming? If we examine young birds kept in complete isolation from conspecifics; isolated, this is, either from the egg or from the early fledgling life, we find a number of instances of birds so treated in which the vocalizations emerge with little or no modification of acoustic structure. This certainly seems to be true of many of the call-notes referred to above. It also seems to be true of some songs. Thus, the American Song Sparrow (*Melospiza melodia*) will produce an almost completely normal song even when it has been fostered from the egg by canaries and allowed to hear only canary song which is entirely different in pattern and in structure (Marler 1967). The same situation seems to obtain with many species, perhaps all species, of the pigeons and doves (*Columbidae*). The acoustic structure — that is to say the tonal quality — of the notes of birds of this family are remarkably similar as we pass from species to species. To put it crudely — almost all doves "coo". But though the "coos" of all doves sound similar, at least on first inspection, we find that no two species the world over "coo" in exactly the same rhythmical pattern or with the same accent. In other words it would be possible to construct a table for identification of the dove songs based upon the numbers of notes in the song, the overall duration, the length of the individual notes, the timing, the rhythm, and the accent. In other words one can often recognise a given species throughout an enormous geographical range, solely by the temporal organisation of the song. A striking example is the Emerald Spotted Wood Dove (*Turtur chalcospilos*). This bird has a mournful song of approximately 20 notes, in a very distinctive pattern. The species is found from Ethiopia, south through Eastern Kenya and Tanganyika to Central Africa, Angola and South Africa. Yet as far as my own experience goes and from all accounts, that of my fellow ornithologists also, the song appears to be absolutely constant throughout this huge range of many thousands of miles. So this species seems to be defined, both for the ears of other members of the species and for the ears of man, by its vocal pattern. The same conclusion applies to many of the simpler songs of doves characteristic of the continent of Europe. Experiments on some of these species (Lade and Thorpe 1964) indicate that the vocal pattern is completely resistant to crossfostering or other means of exposure to alien song patterns during early life.

Another example of this resistance to early experience is clearly provided by the European Cuckoo (*Cuculus canorus*) where obviously the song produced by the male — which is so familiar to us all — is entirely independent of the vocalizations of its foster parent.

As a result of examples of this kind, one is forced to the conclusion that there must exist something in the nature of an innate neural template or system which is fully competent of *itself* to activate and control the motor processes of the vocalization. This has actually been shown to be the case in the domestic fowl by Konishi (1963) who has shown that the bird can develop and maintain the normal repertoire and forms of its vocal signals even though complete deafening has been carried out operatively in the first days of life. In other words, in the call-notes of the domestic fowl, just as, in all probability with those of the song sparrow and the doves, the postulated innate template is fully competent without auditory feedback.

In many other birds, however, we find something less than this full competence; in that while it is not necessary for the bird to have been able to hear the normal song of the species in early life in order to develop its specific vocal signal yet, some relatively non-specific auditory stimulation is required to render the template fully effective. Thus in the Chaffinch (*Fringilla coelebs*) the normal song structure (Fig. 1) cannot

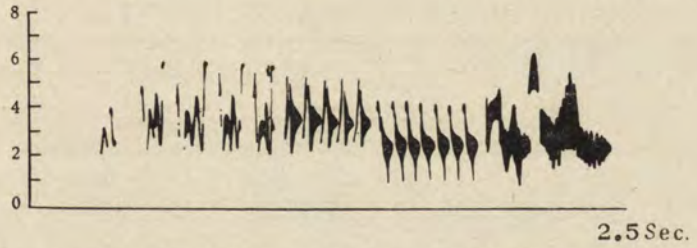

Fig. 1. Sound spectrogram of normal Chaffinch song *Fringilla coelebs*. Vertical scale kc/sec; horizontal scale 2.5 sec

be produced if the bird has been operatively deafened as an early juvenile. The overall song structure — what one might call the 'sound skeleton' of the song — which in this species, and a great many other related passerine birds, constitutes the specific vocal signal, is not produced by birds so treated. (Though again, some call-notes seem unaffected by this procedure of deafening, see Nottebohm 1968). However, once the "normal" song structure and patterning has been allowed to establish itself in the natural manner, operative deafening at a later stage in the life does not affect the performance and maintenance of this song pattern. Thus

here the innate template requires development by an auditory experience which is in at least some respects specific if the normal song is to be produced. But even the stimulus of a very poorly organised — or almost completely disorganised — vocalization from another Chaffinch can have the result of, so to speak, canalizing the song into its right channels. Thus it has been shown that (Thorpe 1958, 1961) even if hand-reared birds kept in acoustic isolation from experienced members of the species, instead of being isolated singly in a soundproof chamber, are isolated in groups of young birds all equally deficient in experience, the experience of singing in concert with the other deprived birds helps these individuals to a significant degree along the path towards normal vocalization. Thus it appears that in this species we do have an innate template present in the brain, but that by itself, without any auditory experience, this template cannot express itself in full control of the motor pattern of vocalization. But if there was no such template and it were all a matter of imitation then quite clearly the specific song of the Chaffinch would not be as stable as it is. A good instance of this is given by the introduction of a few Chaffinches to South Africa in 1900 and New Zealand in 1862. Thus the Cape Town birds and those in New Zealand still produce a song pattern which is clearly that of the Chaffinch. After 60—100 years the basic song structure has not drifted substantially away from that characteristic of the ancestral population of Europe. If everything were imitatively learnt it is almost inconceivable that this would be the case.

The next stage in the adjustment of an innate template by external stimulation, and the first step in the replacement of the innate system by a response acquired by imitative learning, is where an inborn template requires some specific, as distinct from non-specific, external stimulation to render if fully effective. That is to say at this point some imitative learning enters, being necessary even to maintain species distinctiveness of vocal signals. This situation is found in a number of species of "finches" and in some of the buntings. Marler (1967) lists the Arizona Junco (*Junco phaeonctus palliatus*), the White-crowned Sparrow (*Zonotrichia leucophrys*) the Black-headed Grosbeak (*Pheucticus melancephalus*) and the Oregon Junco (*Junco oreganus*). In some of these and other such birds the imitative contact may be minimal for effecting the maintenance of the species distinctiveness I(a) above, but important for I(b) about — which is to produce and maintain group distinctiveness of vocal signals. The last species mentioned, the Oregon Junco is peculiar in that the situation found in many othere is in some degree reversed. That is to say the birds seem to acquire the overall song pattern by imitation, but the syllabic structure of the songs seems to depend on the birds having at their command a great variety of units of vocalization which can be

employed to fill out or complete the song. This process suggests improvisation or "invention" and can itself be increased and developed by imitation.

As our knowledge extends there will probably be found an almost infinite gradation of combinations of these factors in different species. But it is certain that this combination of innate neural mechanism and experience can, in species like the Chaffinch, produce a self-sufficient mechanism; in that if the bird is subsequently deafened it will nevertheless, now continue to sing the normal song without change. And in the unoperated birds the whole singing behaviour may, by this device, become fixed and unalterable after the first peak of testosterone production has been reached in the first breeding season. Thus in the Chaffinch we find that learning of refined details of song is at its maximum early in the first spring — namely when the bird is about 8 months old — and increases up to a peak at about 14 months after which it ceases entirely. What the bird has learnt by the age of 14 months constitutes its song or songs for the rest of its life. Thus there may be one fully developed song pattern or as many as six according to the number and/or song variety of adult males competing in the auditory environment in which the bird has developed.

The mechanism that I have just outlined is appropriate firstly to produce and maintain the group distinctiveness of vocal signals, and also to allow of individual distinctiveness without spoiling the specific distinctiveness. That is to say the bird by means of the control exercised over its imitative ability maintains the normal outline of the song and the main features of it, but fills in the structure by taking perhaps most of the finer details from its singing neighbours. In this way a group dialect will be produced such that the birds from one locality will tend to approximate to one another in the details of their song, and those from a locality, say 50 or 100 miles away, will tend to have a slightly different average pattern of fine details. Within the vocal dialect it allows the individual birds to develop their own peculiarities of song so that the song can now serve *three* purposes: specific distinctiveness, group distinctiveness and individual distinctiveness of local signal. An interesting case of this is shown by the songs of the Bou-bou Shrikes (*Laniarius aethiopicus major*) depicted in Fig. 2 and 3 (Thorpe and North 1965, 1966, Thorpe 1966). Here the two members of the pair learn to duet with one another and while adopting certain phrases and rhythms which are characteristic of the locality, they will work out between themselves duets which are sufficiently individual to enable the bird to distinguish and keep in contact with its mate by singing duets with it (or, to be more exact, by singing *antiphonally* with it) in the dense vegetation in which many of these

birds live. In some species no doubt the vocal quality alone may suffice to distinguish a species and in that case the imitative and inventive powers of the birds can be used if necessary to produce a completely into distinguish a species and in that case the imitative and inventive restrict these to the task of copying members of their own species, and

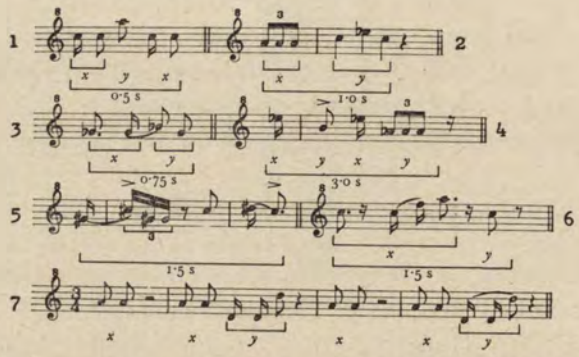

Fig. 2. Seven examples of antiphonal song of the tropical Bou-bou Shrike (*Laniarius aethiopicus*). Letters *x* and *y* indicate the contribution of two different birds. (Reproduced by courtesy of the Editor of *Nature*. From Thorpe and North 1965.) 1, *L. aethiopicus sublacteus*. Vipingo, Kilifi, Kenya, December 1954. N. B. All the illustrations are given at approximately scientific pitch (middle C = 256 c/sec.) Unless otherwise stated, as here, all figures refer to race *major*. 2, *L. aethiopicus*. Dundori, Nakuru, Kenya, March 17, 1964. 3, *L. aethiopicus*. Kabale, Uganda, February 15, 1962. 4, *L. aethiopicus*. Meadow Point, Lake Nakuru, Kenya, March 17, 1964. 5, *L. aethiopicus*. Hippo Pool, Lake Nakuru, Kenya, March 17, 1964. Note that this is a rather more elaborate duet than the previous ones. The contribution of the two birds is not indicated in this case since it seemed to vary a good deal. 6, *L. aethiopicus mossambicus*. San Martino, Mozambique Coast (C. Haagner). The timing in this example is very precise, but the bar length might vary between 0.7 and 1.5 sec. 7, *L. aethiopicus mossambicus*. San Martino, Mozambique Coast (C. Haagner). This is a duet with a more complex time pattern. Bar length 1.5 sec

do not, even in captivity, mimic other bird species — still less man himself. But as everyone knows, there are such bird mimics, of which the Mocking Bird (*Mimus polyglottis*) is a well known example in the United States, and the Starling (*Sturnus vulgaris*), Blyths Reed Warbler (*Acrocephalus dumetorum*) and the Marsh Warbler (*Acrocephalus palustris*) in Europe. These birds are something of a puzzle since it is not at all clear what biological advantage is achieved by imitating other species. The Indian Hill Mynah (*Gracula religiosa*) however, shares with parrots the peculiarity that while supreme imitators in captivity (Thorpe 1967), they have never been heard to imitate any other bird or animal in the wild. Thanks to the studies of Dr. B.C.R. Bertram in Assam (whose yet un-

published work I am grateful to be allowed to quote) we are now beginning to understand the situation in this very puzzling case. It appears that these Mynahs do, in fact, imitate other Mynahs but the calls show such a wide range of patterns, and the differences between them are, to the human ear, so subtle that imitation is undetectable without close study of neighbouring individuals by tape recorder and sound-spectrograph. When, however, these birds are handreared they seem to imprint very easily and thus they imitate all sorts of noises in their environment particularly the noises most closely associated with human beings. Hence their fame as mimics. Dr. Bertram's analysis of data obtained in India has confirmed his general conclusion found during field work namely, that Mynahs have four categories of vocalization types, two being species specific, one unique to the individual, and the fourth a repertoire of loud calls unique to the locality. No bird shares calls with its mate, but all have most calls in common with a few near neighbours of the same sex; there is an extremely rapid dialect change with distance; the sex and home of a given bird can therefore be deduced from the calls its makes. The repertoires apparently stay constant in composition and proportions from year to year. There is a considerable ordering of the sequence in which a bird's calls are made; and they tend to repeat their own call types, make standard replies to those of their mates, and match calls of their neighbours. They respond more strongly to playback calls of neighbours than to those of strangers, and can distinguish at least some of the calls of their mates from nearly identical ones of neighbours.

We come now to a problem where the emphasis is somewhat different.

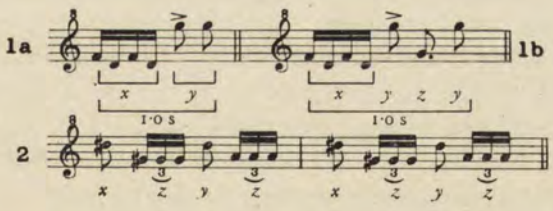

Fig. 3. Three further examples of antiphonal song in *Laniarius aethiopicus*. (Reproduced by courtesy of the Editor of *Nature*. From Thorpe and North 1965.) 1ab, *L. aethiopicus*. Lake Bunyoni, Kabale, Uganda, February 14, 1962. (a) represents a duet pattern heard as a very long, precisely timed series. During one considerable stretch of this series a third bird Z joined in. It was far away from the others, but nevertheless inserted its single note remarkably accurately (b). It tended to intervene in every second duet of *x* and *y*. 2, *L. aethiopicus*. Dundori, Nakuru, Kenya, April 3, 1964. A remarkable trio. All three birds were in the same tree. Note that bird *x* gave a *D* sharp every 2 sec and bird *y* a *D* sharp every other 2 sec, while bird Z gave a *G* sharp and an *A* natural every other 2 sec in alternation

Successful social organisation in animals often requires a capacity for mutual recognition at some distance, between mates and also between parents and off-spring. That is to say, it is often necessary not only for adults to recognise specific characters of their young, and vice versa, but also for them to know one another individually so that parental care and familial organisation and cohesion can operate. So far I have been discussing birds in which the young must be cared for or maintained in a nest by the parent. When such nidicolous birds leave the nest they tend to stay together, return to the nest to be brooded and so remain in the territory. It follows that it is not necessary for the vocalizations of the young to be individually recognised by the parent. The young will simply easily be found by looking at familiar branches or twigs in the neighbourhood of the nest and leading them back to the nest when the weather or the hour of the day necessitate brooding. In colony nesting birds, individual recognition is highly developed in those species where the young have to be cared for or maintained by the parents some time after fledging. This brings us to Section II of my outline classification; namely the ability to recognise the signals and produce the appropriate responses in each case. (What follows is largely taken, by kind permission of the Editor of *Nature*, from my article of 1968).

When we consider the problems of reproduction and survival faced by birds such as many species of gulls, terns, gannets, penguins and so on — birds which nest in very dense colonies and obtain their food during the nesting period in rather restricted areas of sea or coastline near the colony — we can at once see a number of ways in which such abilities for individual recognition could be advantageous. Without individual recognition, the feeding of the young, at least as soon as they become mobile, could be a very wasteful process. Hordes of young would be competing for food from each individual adult as it returned to the colony; with the result that the strongest, the most fortunate, the most mature or the quickest, would obtain ample food and many others would starve. In other words, there would be a wasteful struggle among the young to reach the returning adults. Again, it is often important that the parent should bring food — for example, fish — of the right size for its young of a given age: a fish 3 inches long may be too large for a small chick to swallow; whereas occasional meals of fish 0.25 inches long result in undernourishment of the larger chicks. Similarly, it is often apparent that the smaller young receive a different kind of food from that brought to the larger ones. So both size and quality vary with age. The same problem arises in the brooding of the young birds especially during bad weather. If all was haphazard, some young would get too little brooding and some too much which would presumably result in

disastrous mortality in the young birds as a whole in the colony. Later still in the life-cycle, when the young are nearly ready to fly or are first flying, it may be necessary for them to follow a particular parent rather than to accompany anonymously a flock of adults. Following an individual parent will give the young bird a much better opportunity to learn by experience how to find places where the right food can be obtained in quantity, and how to learn the best way of collecting and consuming it. Again, as is usual in mammals, parental care is of immense importance in protecting against predator attack and learning to avoid it.

That nest-site and mate-fidelity are indeed of adaptive value in enhancing breeding, success has been demonstrated by the work of Coulson (1966ab) on the Kittiwake (*Rissa tridactyla*). He found that a female which retained her mate from the previous breeding season bred earlier, laid more eggs and had a greater breeding success than one which had paired with a new male. More recently it has been shown (Ashmole and Humbertotovar 1968) that parental care in sea birds may be much more prolonged than has hitherto been thought, and, of course, parental care can only be achieved if there is mutual recognition.

It is obvious that if the visual powers are sufficiently well developed, vision will probably provide a larger number and greater variety of cues for recognition than any other sense. But it also seems certain that in birds just as in primates, because of the greatly varying conditions of visibility, lighting, apparent size, and angle of approach, the problems of perceptual constancy are very acute indeed. The effect on visual perception of the almost incessant and quite unpredictable changes in the quality and intensity of the light must be enormous. That is to say, the visual responses of sea birds must constantly be at the mercy of dazzle, fog, cloud and, of course, darkness.

Consequently, it is obvious that if another sense could be used for recognition which does not involve such great perceptual constancy difficulties, either in addition to or in place of vision, there would be a great selective advantage in making use of it. So the questions arise: how far can the auditory sense serve the purpose? Is the acuity and complexity of auditory perception great enough? And is the individual sound production of the birds sufficiently constant to the individual and sufficiently distinct from other individuals to allow such a system to operate? First, it is likely that if sounds can be used, the message they carry is far less liable to distortion and interference than the visual patterns received by the eye from a distance. Sounds can be masked by loud random noise, such as that of wind and sea and the hubbub of the colony, although even here the so-called "cocktail party" problem and the studies of it which have been made (Cherry 1957, p. 277, Gibson 1968, p. 87) show

that, in human beings at least, a particular sound pattern which is being listened for can be detected with extraordinary precision in conditions of apparently overwhelming interference. The only factor producing definite distortion is the Doppler effect whereby, of course, the pitch and overall duration of the sounds are changed according to the speed of approach or recession. This, however, is not likely to be a very serious difficulty in the circumstances in which recognition is likely to have to operate with colonial nesting birds; and would scarcely be comparable with the effect on vision of changes in illumination. The only important advantage which vision seems to possess is the precise directional adjustment and focussing power of the eye whereby the gaze can locate and track the object and so maintain fixation.

As to the parameters which are available for recognition in a complex sound, they are much greater than might at first be expected. A pure tone, it is true, can be experienced only by neglecting transients and ordinarily only with an artificial stimulus. There are very few pure tones in nature. Meaningfully patterned sounds, however, vary in much more elaborate ways than simply in pitch, loudness and duration. To quote Gibson (1968, p. 87), such sounds "instead of simple duration vary in abruptness of begining and ending, in repetitiveness, in rate, in regularity of rate, or rhythm, and in other subtleties of sequence. Instead of simple pitch, they vary in timbre or tone quality, in combinations of tone quality, in vowel quality, in approximation to noise, in noise quality and in changes of all these in time. Instead of simple loudness they vary in the dimension of loudness, the rate of change of loudness, and the rate of change of change of loudness. In meaningful sounds, these variables can be combined to yield higher order variables of staggering complexity. But these mathematical complexities seem, nevertheless, to be the simplicities of all auditory information, and it is just these variables that are distinguished naturally by an auditory system".

(a) *Colony-nesting Birds.* Now as to birds, there is already strong reason for suspecting that the adults of the Common Tern (*Sterna hirundo*) can recognise their mates and young — and the young their parents — by call alone (Tinbergen 1931, Palmer 1941). Similarly with the Herring Gull (*Larus argentatus*), Tinbergen (1953) recorded that the sleeping gull is awakened by the long-drawn "mew" of its mate, although the same call uttered by any other bird leaves the sleeping individual quite unconcerned; again, Stonehouse (1960) gave a remarkable account of the way in which the young of the King Penguin (*Aptenodytes patagonica*) in their densely packed "crèches" respond only to their parents' call when these return to feed their young. But the best published evidence to date comes from the studies of Tschanz (1964). This worker has shown

that the young of the Guillemot (*Uria aalge*) may react selectively to the calls of the parent even during the first few days of life and that the parents similarly recognise their young. He has also obtained positive results from experiments with tape-recorded calls and has provided some oscillographic evidence for individual differences in the calls of the adults. The oscillograph is however, not a satisfactory tool for such studies which involve highly elaborate patterns of sound, and I felt that further investigation was badly needed; particularly in view of the fact that in no single instance hitherto has there been any indication of the kind of acoustic differences on which recognition can depend. We have found (Hutchison et al. 1968) that, with the Sandwich Tern (*Sterna sandvicensis*), the so-called "fish-call", uttered by the returning parent bird bringing food to its young, has just the kind of structure required to provide auditory data for individual recognition and that in the forty different individuals with which it was possible to obtain a series of samples of the "fish-call" each bird had a call measurably distinct from all the others, and the calls issued by any one bird were extraordinarily constant to that bird. Fig. 4 shows the sound spectrograms of typical recordings of two consecutive calls of three different individuals of the sandwich tern. Table I gives correlation between successive calls of twenty individuals.

Table I

Correlations between successive calls of twenty individuals of the sandwich tern

Measure	Correlation coefficient*
Total duration	0.98
Duration of segment *a*	0.92
No. of vertical bars in segment *a*	0.82
Duration of segment *b*	0.94
Lowest frequency in segment *b*	0.95
Duration of segment *c*	0.98
No. of vertical bars in segment *c*	0.98

* All significant at less than the 0.01 level.

Having provided this evidence that each Sandwich Tern has its own individual "fish-call", we must ask the question: if other birds of the same species were to identify an individual's call, which features might they use? If the variation of a particular characteristic were large it would presumably be easier to discriminate differences between birds than if the variation were very small. Further more, if two measures of

a particular characteristic have about equal variation, and the mean of one measure is smaller than the mean of the other, the psychophysical data obtained from experiments with human subjects suggest that it might be easier to discriminate differences over the low absolute values. For example, if the standard deviation were 1 sec, it would be easier to discriminate this difference from a mean of only 1 sec than from a mean of 100 sec. Thus, the standard deviation weighed by the mean value of a measure should give a ratio for which low values indicate small variation and/or a large mean, or a difficult measure to discriminate; and high values indicate an easier measure to discriminate. If we assume that a similar rule can be applied to the Sandwich Tern, then the largest values of the ratio *standard deviation of measure/average value of measure* with respect to a particular characteristic (for example, duration) would suggest the most likely sources of discriminable inter-individual differences. It could also be argued that the measure having the smallest values of this ratio might indicate the features which identify a call as that of *Sterna sandvicensis*. This ratio was obtained for each measure (Table II).

Table II

Ratio of standard deviation over mean for forty individuals

Measure	Ratio
Duration of segment *c*	5.85
No. vertical bars in segment *c*	3.62
Lowest frequency of fundamental of segment *b*	3.09
Duration of segment *b*	1.81
Total duration	1.74
Duration of segment *a*	1.55
No. bars of segment *a*	0.52

Because the duration of segment *c* has a higher ratio than the other three duration measures, and because the number of vertical bars in segment *c* has a higher ratio than the number of bars in segment *a*, it is more likely that both duration and number of bars in segment *c* are used to identify an individual's call than are those measures in other segments. Finally, the lowest frequency of the fundamental of segment *b* has a high ratio, and if terns are fairly sensitive to change in frequency then this, too, might contribute to the discrimination of calls of different individuals.

Thus, because individual calls are correlated, it is possible that calls are used as a basis for identification among individuals and three or four possible features can be suggested which might be used in making such an identification. Observation of the behaviour of the young Sandwich

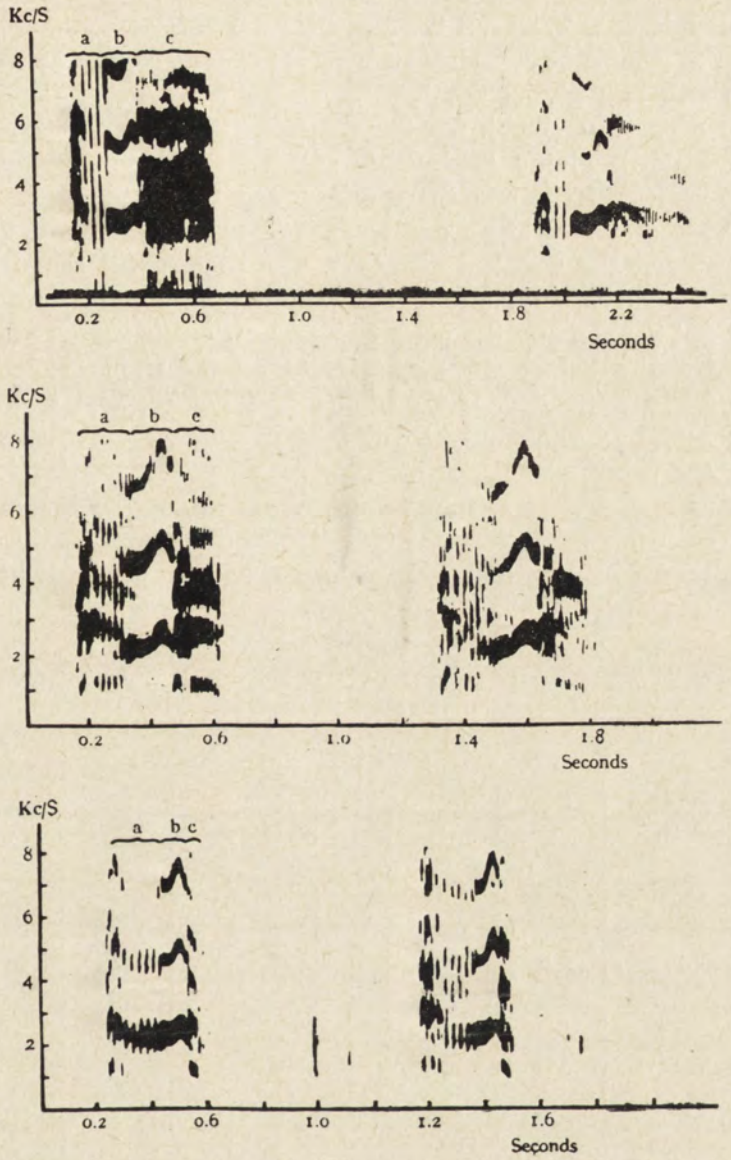

Fig. 4. Sound spectrograms of typical recordings of two consecutive calls of three different individual Sandwich Terns. Note that each call is divided into three segments *a*, *b* and *c*. Segment *a* contains anything from seven to fifteen vertical bars which indicate brief pulses of sound of great frequency range. Segment *b* shows the fundamental and usually two harmonics rising and falling during the duration of the phrase of 0.07 to 0.15 sec to give an inverted *v* or inverted *u* pattern. Segment *c*, of duration between 0.01 and 0.28 sec, again shows vertical bars varying in number from three to twenty-eight and showing peaks of intensity at particular frequencies rather than the very wide and uniformly distributed frequency range displayed by the bars in segment *a*

Terns which have already left the nest for 5 days or more and are wandering about in groups of considerable size shows clearly that adults returning with fish and giving the "fish-call" are not looking for particular young in a particular spot. On the contrary, they are flying round and round low down giving "fish-calls" all the time as if expecting the young to appear. Here and there one young bird will get particularly excited by the arrival of an adult carrying fish, whereas all the young nearby pay not the slightest attention. The parent will sometimes land and look around when a young one may come running towards it, or this may not happen and the parent will go off on its search again. Some time may elapse before what appears to be the right chick has been found and has responded. If the young does not respond to the parent it is impossible for the adult bird to feed it. These observations and our work on the sound signals of the returning adults were carried out at Scolt Head Island, Norfolk, in 1966 and 1968. There were more than 2,000 pairs in the colony, so patterning of the different features of the "fish-call" must play an important part if it is, as it seems to be, providing a reliable basis for audio-recognition.

Table III

Measurements of the sound spectrograms of five individuals which called twice while flying over the hide

Bird no.	Total duration (s)	Segment duration (s)			No. bars		Lowest frequency of fundamental kHz
		a	*b*	*c*	*a*	*c*	
51.1	0.31	0.18	0.10	0.03	14	3	2,200
51.2	0.32	0.18	0.10	0.04	14	6	2,200
59.1	0.31	0.16	0.09	0.06	10	8	2,300
59.2	0.31	0.16	0.09	0.06	10	6	2,300
54.1	0.30	0.18	0.07	0.05	13	6	2,200
54.2	0.32	0.18	0.07	0.07	13	6	2,250
57.1	0.34	0.22	0.09	0.03	11	3	2,100
57.2	0.34	0.22	0.09	0.03	11	3	2,200
69.1	0.33	0.21	0.09	0.03	10	3	2,300
69.2	0.33	0.21	0.09	0.03	12	3	2,300

Table III provides an illustration of the subtle combination of characteristics involved, measured from five individuals which have calls differing in total duration by only 0.01—0.04 sec.

In summary, we can say that, while the extent to which these separate individual characteristics are recognised as distinctive by birds

themselves has not been investigated, it is clear that if the "fish-call" is used, as it seems to be, as an effective means for individual recognition in a large colony of 2,000 or more pairs, patterning of the call (in the sense of the "gestalt" or the overall relationship of the component parts) must play an important part.

In 1967 we carried out a pilot investigation of the individuality of the calls uttered by returning adults of the Gannet (*Sula bassana*) on the Bass Rock, East Lothian, Scotland (unpublished results of S. J. and R. E. White and W. H. Thorpe). In this species, too, there is considerable evidence from field observation that individual recognition by voice can occur. Here the problem is somewhat more difficult in that returning calls of the Gannet do not have the clear division into three sharply defined sections that is found in the Sandwich Tern, and it has not yet been possible to establish the clear differences of frequency-time pattern in the Gannet which is found in the Sandwich Tern. Nevertheless, the striking fact has emerged that if the profile of amplitude variation with time is studied rather than the normal sound spectrogram then consistent differences are displayed just as in the Sandwich Tern. Thus, to date, five landing calls of four individuals have been fully analysed. Each full call is made up of a series of components which are fairly similar. The analyses were made by tracing the amplitude display of a full call onto graph paper. For each component, ordinates were measured at intervals of 0.01 sec (approximately 1 mm); corresponding measurements were averaged to give an overall "profile" of a full call. Each "profile" was compared with every other to obtain a Pearson correlation coefficient (r). Very high coefficients (> 0.90) were obtained with comparisons between calls of the same individual, and lower coefficients (< 0.70) were obtained by comparing calls of different individuals.

There was also a tendency for there to be characteristic differences in length of the component calls, although the timing between sounds was variable.

It is not, of course, necessary to suppose that the birds in this case rely solely on the pattern of amplitude variations with time which we have so far detected — there may indeed be other possibilities involving pitch discrimination which are also being used, and these possibilities are being investigated further. Nevertheless, the same opportunities for individual auditory recognition seem to be available in the Gannet as in the tern.

(b) Mammals. It is fitting to conclude with a brief summary of the situation in mammals. While there is much that is suggestive of individual recognition by means of vocal signals firm evidence is as yet very sparse indeed. It is probable that individual recognition by this means occurs in primates, but apart from circumstantial evidence for the Rhesus

Monkey (*Macaca mulatta*) (Rowell and Hinde 1962) and the Night Monkey (*Aotus trivirgatus*) (Moynihan 1964) there seems to be nothing in the literature which is at all convincing. It is, of course, among the marine carnivores (*Pinnipedia*) — namely, the seal and walruses — that, because of the existence of huge breeding colonies on the seashore, conditions similar to those under which marine birds so often breed are found. The investigation of vocal communication in mammals is complicated by the existence of ultrasonic hearing in so many mammalian forms, and only recently have techniques been devised for assessing the significance of complex ultrasonic emissions. Nevertheless, it seems clear that the Northern Fur Seal (*Callorhinus ursinus*) recognises its own pups first by smell and that this recognition is later confirmed by voice (Laws 1964). A great deal has been written and many incautious statements made in recent years about the vocalizations of the *Cetacea* — the whales and dolphins. That there is a great deal of communal vocalization in the form of whistles, squeals, grunts and so on, is now fully established (Norris 1963). Quite apart from the sounds used for orientation and probably for echo-location, evidence seems to be accumulating for individuals within a troop or school answering one another, and Caldwell and Caldwell (1965) have shown that with a group of five freshly captured individuals of the Bottle-Nosed Dolphin (*Tursiops truncatus*) consisting of two adult females, one adult male and two sub-adult males, the five predominant whistles for the five animals were clearly distinctive from each other at one-eighth speed. Much remains to be done and these authors are following up the subject; but these results seem to show that there is a definite tendency towards an individualised whistle. Apart from the whistles of this species there is a great variety of other vocalizations — some clearly used for echo-location, some supposedly indicative of the emotional state of the animal — but no critical work on the possibly individual characters of these sounds has yet been undertaken. Finally, with social ungulates, Tschanz (1962) failed to establish auditory recognition between ewes and lambs of the Mouflon Mountain Sheep (*Ovis aries musimon*) although they established clear recognition by smell at 12 hr and by sight from the third day on.

CONCLUSION

In conclusion, it should be pointed out that in man language is of course, the prime vehicle for the necessary transfer of social information. There has perhaps in the past been too much readiness to use the term "language" for the vocal-auditory transmission of information amongst animals. Nevertheless, in spite of the dangers of this nativistic view of

language, such usage has recently been supported by two well known students of human language (Chomsky and Lenneberg 1964). As a result of these and subsequent studies by many others Teuber (1967, p. 205) has said "it has become clear... that linguists are ethologists, working with man as their species for study, and ethologists linguists, working with non-verbalizing species". This I think is a fitting conclusion to our discussion of these remarkable powers of imitation and the use to which they are put by birds and other animals. But it is worth pointing out that whatever imitative ability there may be in birds such as the Terns (*Sterna hirundo* and *sandvicensis*) — and it may be very small indeed — it must be under strict control or otherwise the individual terns in the colony would not have the very great individual distinctiveness of voice that we find. In other words, the problem here is to inhibit or control the imitative powers in certain circumstances and to maximise tendency to produce individual peculiarities of voice. This shows that the motor learning involved in the production of sound signals is an entirely different process from the perceptual learning involved in recognising the signals and in certain species the two must be kept very strictly apart. And finally, this work on the vocal communication system in the sea-birds emphasises very strongly the great importance of auditory powers as the perceptual basis for group organisation. Clearly the young must have an extremely high capability for learning the individuality of their parents' calls, and the adults the same capability for learning the individuality of their mate's calls. But they *must not* imitate them slavishly. If they imitate at all they must imitate the component parts and then randomise them! But perhaps for this task pure inventiveness would be better!

SUMMARY

The vocal signals which constitute the 'songs' of birds are adapted primarily by genetic programming and secondarily by imitative adjustment to some three main functions. 1. To distinguish the species from other species. 2. To distinguish a group of associated individuals (pair, family or local groupings of breeding birds etc.) from other similar groups in adjacent or more distant groups by the establishment of a local 'dialect'. 3. To distinguish one individual more or less certainly from all others in a population. These ends may be accomplished in different species by differences in the degree of competence (or independence from environmental stimulation) of the innate neural template for song structure. Thus the degree of individual experience necessary to develop the full song by addition to and adjustment of the innate template may range

from nil, or minimal on the one hand to something near totality on the other. The song of some species (e.g. the Chaffinch *Fringilla coelebs*) can be so precisely controlled and adjusted by exactly controlled use of the imitative faculty, that it can serve all these three functions at the same time.

In certain species such as those sea birds which nest in dense colonies individual recognition (3) is combined with specific recognition (1) to more or less complete exclusion of group distinctiveness (2). The considerable advantage which recognition based on acoustic signals offers as against visual recognition for this purpose, and especially under the difficult conditions imposed by life in dense colonies on the sea shore, is described and discussed.

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Acta Biol. Exp. 1969, 29: 271—291

Lecture delivered at the scientific session held in commemoration of the 50th anniversary of the Nencki Institute

December 1968

MECHANISM AND LOCALIZATION OF CONDITIONED INHIBITION

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In spite of considerable experimental and theoretical progress of our knowledge on the inhibitory processes in the higher nervous activity, this important field remains insufficiently explored and, in certain aspects, still obscure. Pavlov justly called the problem of inhibition an "accursed problem", expressing thus his annoyance with its complexity and difficulty.

One of the least clear problems is the physiological mechanism of the formation of the internal or conditioned inhibition and the question of its localization within the conditioned reflex arc. The present paper is devoted to these two problems. Since the original views of Pavlov are seldom presented in full even by his followers in current scientific publications, it seems proper to begin with a brief summary of his theory.

At the background of Pavlov's view on the mechanism of conditioned inhibition lies his original concept of the protective and restorative role of supralimit inhibition. "One could think", he wrote "that specific internal inhibition is also a supralimit inhibition, where, however, the duration of stimulation replaced its intensity" (Pavlov 1949, vol. III, p. 608). To put it briefly, the cornerstone of his theory of the physiological mechanism of the development of conditioned inhibition is the assumption that cortical cells, being extremely reactive and possessing high nutritive demands, become fatigued, functionally disrupted and this creates a prerequisite or even a stimulus triggering the development of inhibition. The

inhibitory process is considered here as an active, by nature, and "economic", by character, natural protective and restorative process. From the fact established in his laboratory that the unconditioned stimulus (US) exerts a powerful inhibitory influence (a negative induction) upon the cortical cells of the conditioned stimulus (CS) Pavlov arrived at the following conclusion on the mechanism of the reinforcement. The adequate US, which follows the CS, inhibits by induction the cortical cells of the latter and protects them from functional exhaustion securing thus the maintenance of the conditioned reflex (CR). Omission of reinforcement, i.e., presenting the CS alone, leaves the cells of the CS for a long period in a state of trace excitation and results in their exhaustion. Repetitive nonreinforcement causes that the cells to become exhausted sooner and more profoundly. It should be stressed, however, that considering this functional disruption as a necessary antecedent condition or agent eliciting the inhibition Pavlov was far from identifying exhaustion with inhibition.

It remained unclear how the supralimit inhibition is being transformed into conditioned inhibition and particularly into its various chronic forms. Pavlov did not express any elaborated view and one could only indirectly extrapolate, not without reservations, from his more general remarks concerning the formation of the conditioned inhibitory reflexes and from his ideas of transformation of the excitatory process into inhibition.

Pavlov stated on many occasions that conditioned inhibition develops and is located within the cortical cells of the CS. This point of view was principally based on the wealth of data provided by his co-workers (Babkin 1904, Perelzweig 1907, Krasnogorskii 1911, Kogan 1914, Anrep 1917, and others) mainly experimenting on the order and duration of the irradiation and concentration of inhibition. More strictly these experiments concentrated around the phenomena of afterinhibition and the relationship between the occurrence and duration of inhibition and the proximity (i.e., similarity) of the tested stimuli to the original inhibitory CS. Another observation which yielded support for this view was the retention of inhibitory significance by the differential stimulus after the positive CS had become transformed from, say, an alimentary signal into the defensive CS or vice versa (Friedeman 1912, Frolov 1922, and others).

It has to be admitted, however, that the question of the localization of conditioned inhibition was less convincingly discussed by Pavlov than his other views on that subject, and remained, therefore, the most vulnerable link in his theory of inhibition. In addition to that, Pavlov seemed to disregard some of the well known facts from his laboratories which contradicted his views. First was the observation that the inhibitory stimulus elicits in animals an active motor response antagonistic to the reaction elicited by the positive CS (Mishtovt 1906, and others). Here

also belonged the fact of asynchronous, non-simultaneous disappearance of different components (e.g., secretory, motor etc.) of the conditioned response in the course of extinction, differentiation and so on. (Voskresenskii and Pavlov 1917, Arkhangelsky 1924, Pavlov and Petrova 1932, and others). Similarly, Pavlov did not take into account some of the results of Perelzweig, Kasherininova and others, which, as we shall see later, had special significance for this problem but did not fit his theoretical scheme.

Pavlov's contribution to the theory of cortical inhibition was enormous. By discovering new kinds and varietes of this inhibition, classifying them, describing the conditions of their training, formulating the principles of their genesis and development, establishing the role of inhibition in higher nervous activity and revealing its protective-restorative role — by all this Pavlov opened a new era in the physiology of inhibition, that ever important field in brain functioning. Nevertheless, Pavlov was very critical and dissatisfied with the actual status of the knowledge on this problem. Characteristically, he used to formulate his ideas on that subject very cautiously and with reservations, and often revised his views explaining this attitude by the paucity of experimental evidence, insufficient knowledge and the ultimate complexity of the problem. "This is why I still refuse to accept any of the presently existing theories of inhibition or to put forth a new one. We employ currently some temporary assumptions in order to systematize our factual material and to plan further experiments" (Pavlov 1947, vol. IV, p. 321).

This unsatisfactory state of our knowledge, as stated above, and the extreme importance of the problem attracted many students both among Pavlov's disciples and the others who presented new ideas either on the entire problem or on some of its aspects.

One of the typical points of departure from Pavlov's original views is a conviction, popular among contemporary specialists in the field of higher nervous activity, that conditioned inhibition appears and is primarily localized not in the cortical point of the CS as Pavlov and his pupils thought (Babkin 1904, Zelenyi 1910, Beliakov 1911, and others), but in one of the further links of the conditioned reflex arc. A great many observation substantiated this idea. Thus Perelzweig (1907) and others have shown that inhibition of the CR caused also a diminution of the reinforcing unconditioned reflex (UR). Kasherininova (1909) found that after establishing heterogeneous CRs to different stimuli from the same analyzer, the inhibition of the CR to any of the stimuli led to afterinhibition only the other homogeneous CRs (i.e., reinforced by the same US). A number of authors (Voskresenskii and Pavlov 1917, Pavlov and Petrova

1932, Fursikov 1924, Anokhin 1968, and many others) described the fact that in the course of extinction or differentiation of polyeffector CRs, their various components disappear with different rates, i.e., not simultaneously. Kupalov and his co-workers (Kupalov and Ushakova 1931, Kupalov 1955) noticed that training of chronic conditioned inhibition resulted in diminution or even disappearance of the intertrial salivation. Asratian and co-workers (Asratian 1941, 1951, 1955ab, 1958, 1963) used an experimental design with conditioned stimuli possesing a double signalling role which switched according to the change of experimental situation; these stimuli in one situation elicited one CR and inhibited the other, while in the second situation inhibited the first CR and elicited the other. Having established a binary CR, i.e., two different CRs elicited simultaneously by the same CS, it was possible to extinguish selectively one CR while retaining the other (Khodorov 1955, Asratian 1961). In conditioned reflexes with such a two-way conditioned connection, the following fact was established; conditioned inhibition of the CR of one direction does not inhibit the CR of the reverse connection (Asratian 1955ab, 1960). In addition to all this, electrophysiological studies ascertained that inhibitory CSs are accompanied by the arousal reaction and elicit evoked responses in the electrocorticogram similarly to the positive CSs (Laptev 1949, Kogan 1956, 1962, Roitbak 1962, Kratin 1967, Rabinovich 1963, Gasanov 1968). In this context some data are also relevant obtained on children and adult human beings showing that the subjects perceive the inhibitory stimuli as well as the positive ones.

Having disagreed with the idea of the cortical cells of the CS as the site of conditioned inhibition the above mentioned authors pointed at several other structures within the CR arc where the inhibition might be situated. Some of them followed the suggestion of Perelzweig (1907) and Kasherininova (1909) and indicated cortical or even subcortical structures of the UR (Anokhin 1968, Pankratov 1955, 1956 and others); others postulated its location in both cerebral structures of signalling and reinforcing stimuli (Kupalov and Ushakova 1931); the third group, to which the author belongs, assumed that the conditioned inhibition develops primarily and is localized within the elements of the conditioned connection itself (Asratian 1949, Skipin 1956, Maiorov 1959, Beritov 1961, Korotkin and Suslova 1962, Voronin 1965 and others).

These discrepancies in opinion concerning the localization of conditioned inhibition are intimately related to different views on the physiological mechanisms of its development, however, even those authors who agree on localization may disagree on the physiological mechanism. It does not seem feasible to present any detailed description of these complex problems but a brief review may prove useful.

Perelzweig, Anokhin, Kupalov, Hilgard and Marquis 1940 and others assume that internal inhibition results from the clash or competition of two different reflexes, i.e., they postulate the mechanism which Pavlov reserved for external inhibition. However, they disagree as to the exact meaning of this competition or interference. Perelzweig spoke of the struggle between the center of the CS and center of the UR; nonreinforcement causes the weakening of the latter which becomes overruled by the former. The remaining authors, if we disregard minor nuances, share a common view that nonreinforcement elicits an orienting reflex and the interference occurs between the excitation residing in the structures of the CR and this orienting reflex. Since these reactions are incompatible the orienting reflex by means of negative induction or according to the principle of "exclusiveness" takes over the CR. When this is repeated the hitherto unconditioned inhibition of the CR becomes established as a conditioned inhibitory reflex.

It is worth while to stress the difference between this and Pavlov's formulation. Pavlov thought that inductive inhibition of neurons of the CS results from the reinforcing stimulus and that this external inhibition prevents the development of the conditioned inhibition. Anokhin, Kupalov and others from this group maintain that *inductive inhibition* (or, using their words, inhibition due to interference or "exclusiveness") of the neurons of the CS appears as a result of nonreinforcement and provides the basis for the development of the conditioned inhibition.

Orbeli (1945) also maintained that the inductive inhibition is involved in the mechanism of formation of the conditioned inhibition but he referred to succesive induction within the excited structures of the CR.

There is a well known concept that the conditioned inhibition is related to the special inhibitory structures — inhibitory synapses, inhibitory interneurones of inhibitory subcenters, which are activated by nonreinforcement and form special inhibitory conditioned connections. Conditioned inhibition is established when these conditioned inhibitory connections prevail over the positive conditioned connections. Among adherents of this concept are Aleksanian (1956, 1958), Sokolov (1958), Konorski (1967), and to some degree Simonov (1962) and others. They disagree among themselves as to which definite structures function as inhibitory ones and as to how they are activated and how the conditioned inhibition develops.

An original hypothesis on internal inhibition was put forth by Beritov and Roitbak (1962). The gist of their concept is, in general, that the omission of reinforcement strengthens the backward conditioned connection and this leads to the activation of the dendrites of pyrami-

dal cells; slow potentials which then appear in the dendrites yield an anelectrotonic suppression of the soma and its synaptic excitatory contacts. Besides, Roitbak assumes the involvement of the non-specific thalamic nuclei.

Recently still other ideas have been published on the development of conditioned inhibition. The role of the diminution in the muscle feed--back impulses from effector organs was hypothesized (Kratin 1967, Rabinovich 1963 and others), or the generation of a local non-spreading excitation in the cells of CS was postulated (Gasanov 1968), etc.

Finally, one can find, among the contemporary workers in this field, those who attempt to develop further the original view of Pavlov, namely, the view that the conditioned inhibition arises from the protective-restorative inhibition which is generated whenever the neurons become exhausted, i.e., "functionally disrupted". Although the very transition of the protective inhibition into conditioned inhibition is interpreted in many ways, the general idea finds the support of many pupils and followers of Pavlov (Fedorov 1949, Pankratov 1955, Asratian 1955a, Skipin 1956, Voronin 1965 and others). Most of them simply reiterate Pavlov's view, except to Fedorov and Asratian who went a little further. Fedorov (1949) ascribes the decisive role to the summation of the effect of CS with the time CR which causes a marked *enhancement* of the conditioned excitation while Pavlov thought that the exhaustion is produced simply by the repetitive *prolonged* trace excitation of the cells in the cortical point of the CS.

Since the present paper is aimed at the presenting our view we shall now procede more deliberately.

Although our ideas divert essentially from the original view of Pavlov, we consider them as a further development of the concept of our teacher. We agree with him that the basis for the generation of conditioned inhibition consists in the inhibition created by the fatigue, exhaustion, or "functional disruption" of the nervous structures devoid of the beneficial effect of the inductive inhibition normally elicited by the UR. We disagree, however, with Pavlov as to which particular elements of the CR arc are exposed to fatigue and exhaustion and consecutively become the very site of occurrence of inhibition. Pavlov thought that it is the cortical nervous cell of the CS that becomes exhausted and therefore in this very cell inhibition is generated, or, to use his words "the inhibitory process arises in the nerve cells themselves and not in the connecting path between those cells excited by the conditioned stimulus and those excited by the special unconditioned stimulus employed" (Pavlov, 1947, vol. IV, p. 323). According to our view elements of the middle link of the CR arc, are subjected to exhaustion i.e., the nervous elements

of the conditioned connection itself, and they are the primary locus of inhibition.

We have already mentioned some of the experimental data obtained in our and other laboratories, which inspired our departure from Pavlov's view on the location of conditioned inhibition. Instead of repeating we shall rather supplement them with some other facts which should not only substantiate our concept but will also help to argue against another commonly accepted view, namely, that conditioned inhibition is located within the cerebral structures of the UR. It is also clear that all the evidence against either the nervous cells of CS or UR as a site of inhibition serves as an additional corrolary for our thesis that the inhibition is generated and localized within the conditioned bond itself.

The following facts seem to have some relation to the problem of localization of the conditioned inhibition. Struchkov (1955, 1964, 1966) succeded in establishing in a dog a situational cross-switching of two conditioned reflexes. In situation 1 a buzzer elicited a food CR whereas the tactile CS evoked a defensive CR reinforced by electric stimulation. In situation 2 (another CR-chamber) the signalling meaning of both CSs was reversed, the buzzer eliciting the defensive CR and the tactile CS signalling food. It was obvious that in both situations neither cortical elements of the CSs nor the points of URs could be assumed as inhibited, so one has to assume that the inhibition was localized in intermediate links of the CR arc.

Several authors from our laboratory (Varga and Pressman 1963, Struchkov 1966, Rudenko, in preparation, and others) trained dogs in conditioned reflexes possessing two-way conditioned connection. To achieve it they paired alternatively two different unconditioned reflexes, for instance, alimentary and defensive eye blink reflex, creating thus the situation where each from the paired USs became a CS for the other US and elicited an appropriate CR. Fig. 1 and 2 show portions of the recordings from the experiment of Struchkov and Rudenko. Fig. 3 represents a scheme of the reflex arc of such a conditioned reflex. The following results from these experiments are of particular interest. After complete extinction of one of these two mutually connected CRs the other one not only remains undisturbed but often becomes increased. Fig. 4 and 5 illustrate this point. Such a result would be not feasible if the conditioned inhibition was located in cortical point of either of the two paired URs.

In conclusion we would like to add that although we propose and support the idea of a primary locus of internal inhibition within the conditioned connection itself, we admit that when the inhibition becomes more intense it could spread towards the cortical points of conditioned and unconditioned stimuli.

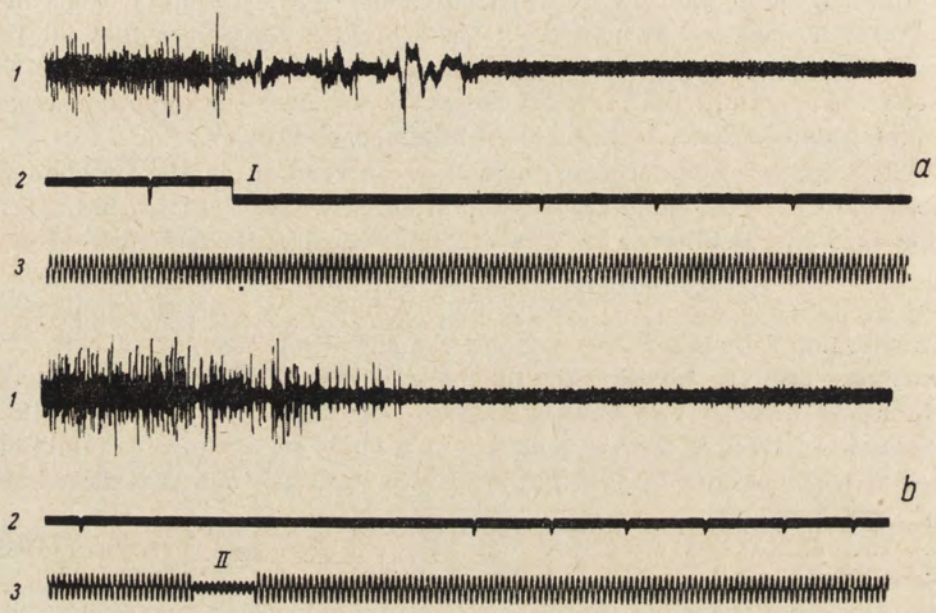

Fig. 1. Conditioned reflex with a two-way connection obtained by systematic pairing of the passive lifting of the leg with food. a, passive lifting of the paw (I) together with the unconditioned disappearance of potentials in the EMG elicits a conditioned salivary response (a forward conditioned connection). b, food (II) elicits unconditioned salivation and in addition causes a conditioned disappearance of the EMG potentials (a backward conditioned connection). 1, EMG. 2, salivation in drops. 3, time (larger deflections) and eating (smaller deflections). From the experiment of Struchkov

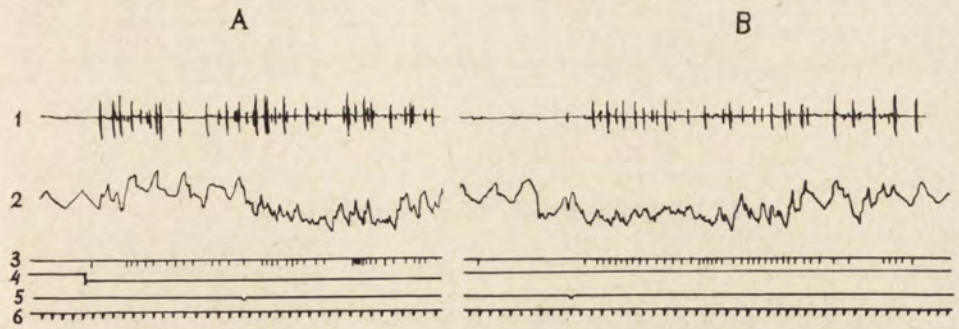

Fig. 2. Forward and backward connections obtained by pairing of two unconditioned stimuli: an air-puff to the eye and food. A, air-puff to the eye evokes the adequate UR, the eye blinking and elicits a CR, salivation (a forward conditioned connection). B, eating produces salivation and elicits conditioned eye blinking (a backward conditioned connection). 1, eye blinking; 2, chest breathing; 3, salivation; 4, conditioned stimulus; 5, delivery of food; 6, time in seconds. From the experiment of Rudenko

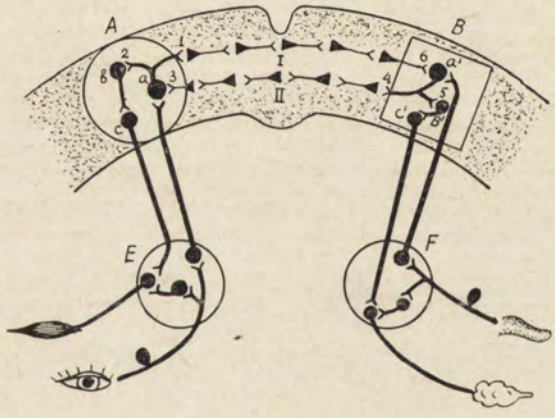

Fig. 3. Schematic representation of the conditioned reflex arc with a two-way connection. A, cortical point of the eye-blink reflex. a, afferent neuron; b, interneuron; c, afferent neuron; 1 and 2, synaptic contacts of collaterals of the afferent neuron with interneurons; 3, synaptic junction between the interneuron of the backward conditioned connection and the afferent neuron of the signalling stimulus. B, cortical point of the food reflex. a′, afferent neuron; b′, interneuron; c′, efferent neuron; 4 and 5, synaptic contacts of collaterals of the afferent neuron with interneurons; 6, synaptic contacts between the interneuron of the forward conditioned connection and the afferent neuron of the reinforcing stimulus. I, forward conditioned connection; II, backward conditioned connection; E, subcortical center of the eye-blink reflex; sub-cortical center of the food reflex

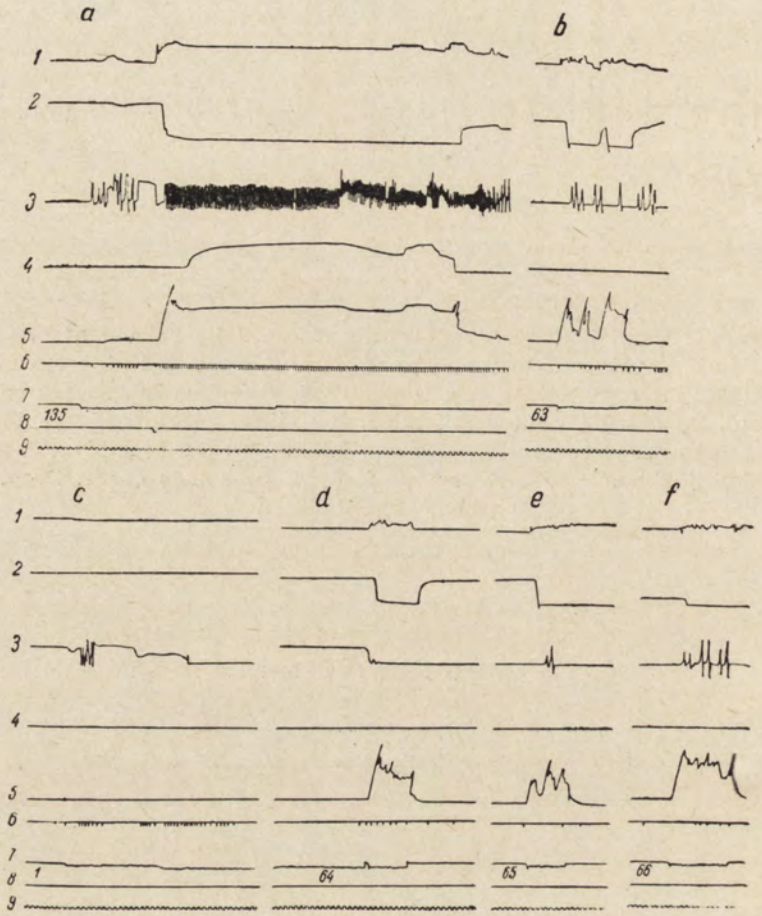

Fig. 4. Backward conditioned connection remains intact after the forward conditioned reflex to a tone is extinguished. a, forward conditioned food connection to the tone of 500 c/sec. b, backward conditioned connection prior to the extinction of the forward CR; c, beginning of the extinction; d, termination of the tone and the first test-trial of the backward CR after the extinction of the forward CR immediately after the last extinction trial of the tone; e, backward CR one minute later; f, same CR four minutes later. 1, movements of the left hindleg; 2, movements of the right (conditioned) hindleg; 3, chewing; 4, placing the paw on the platform; 5, flexion of the conditioned hindleg; 6, salivation; 7, conditioned stimulus; 8, unconditioned stimulus; 9, time in seconds. From the experiment of Struchkov

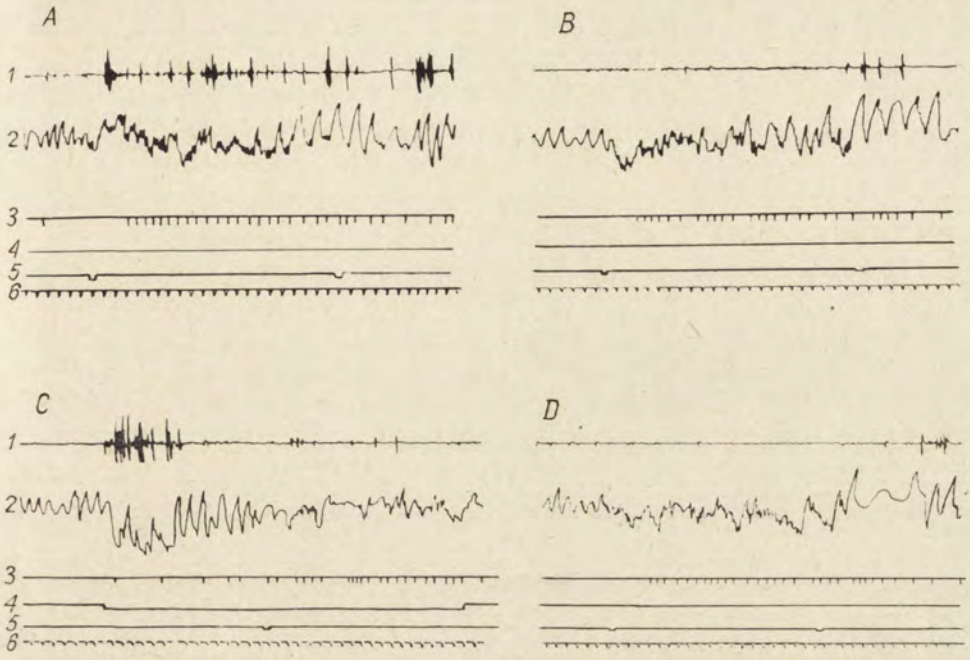

Fig. 5. Forward conditioned reflex after the extinction of the backward CR. A, backward CR (eye blinking) before extinction. B, extinguished backward CR. C, testing the forward CR (salivation) after the extinction of the backward CR; the forward CR remains intact. D, backward CR on the next trial is still inhibited. Other explanations as in Fig. 3. From the experiment of Rudenko.

Before attempting the presentation of our view upon the physiological mechanism of the development of internal inhibition we would like to recapitulate some of the principally important statements of Pavlov, and, in particular, those which were written at the time when he analyzed new facts concerning the formation of a CR with an indifferent stimulus presented not prior but during the US i.e., after its onset. In contradistinction to his views already quoted, Pavlov had to compromise and assumed that "new connections can be established in the cortex, not only in the areas of optimal excitability, but also in those parts of the hemispheres which are more or less inhibited" (Pavlov 1947, vol. IV, p. 325). Moreover, discussing the particular conditions when the CS is applied during the action of the US, i.e., while the latter exerts its inductive-inhibitory effect upon the cells of the CS, Pavlov made an insightful remark: "one has to admit that the mechanism of development of a conditioned reflex and the mechanism of external inhibition are somehow similar, and that the process of external inhibition bears some relation to the development of new connections between different cortical elements" (Pavlov 1947, vol. IV, p. 324).

However, this compromising assumption hardly solved the apparent contradiction. If the inductive inhibition is so shallow that the cells of the CS are still capable of forming new conditioned connections, how it could secure an effective rest and avert their functional disruption? On the other hand, if the inductive inhibition is intense enough to protect the cells of the CS from any fatigue, how could they be capable of participating in any kind of conditioning?

It seems to us, though, that the facts which prompted Pavlov to make those amendments to his original concept, could be explained without sacrificing his notion on the mechanism of generation of internal inhibition. As such an explanation we propose our hypothesis of *the intermediated inductive inhibition of the elements of the conditioned connection by the reinforcing unconditioned reflex.*

To make this concept more explicit we shall use our scheme of the CR arc possessing the two-way conditned connection, as presented in Fig. 3.

By pairing two different URs in various temporal relations, we have been able to investigate in much detail the fate not only of the newly developing conditioned reflexes but also of the adequate inborn unconditioned responses elicited by these stimuli. Some of the facts, obtained during our longlasting studies, have already been mentioned. Other observations, which are directly related to the question of internal inhibition will now be discussed.

We have analysed extensively the well known fact of diminution of the orienting reflex to the stimulus which becomes a conditioned signal. This phenomenon was particularly striking in the experiment of Erofeeva (1913) who trained a food conditioned reflex in dogs to the electric stimulation of the paw. Similarly, in our experiments the adequate unconditioned response to the stimulus which served as a CS, be it defensive-motor response, alimentary reaction, eye blinking or a local vaso--motor reflex, decreased invariably at the same time when the conditioned response appeared. This diminution of the adequate response (for the CS) was accompanied by the lengthening of its latency and threshold elevation. Fig. 6 and 7 show examples of such changes during the experiments of Varga and Rudenko.

These and similar observations were explained by us by the repeated development of the inductive inhibition resulting from the reinforcing US and localized within the intermediate link of the UR arc of the first, i.e., signalling stimulus. In Fig. 3 it is synapse 2 between the afferent and intercalate neurons within the arc of this reflex. This fact could not be explained by postulating the inductive inhibition of the afferent link of this reflex arc (i.e., neuron *a* on Fig. 3) and there are also other obser-

vations which clearly contradict it. Thus, if the indifferent stimulus is presented during eating but is additionally reinforced with a new portion of food, it becomes a food CS (Kasianov 1949, Zbrożyna 1958). The intensity of the CR depends on the duration of simultaneous presentation of conditioned and unconditioned stimuli (Maiorov 1928, Rokotova 1956, and others). Moreover, it has been found in our laboratory and by other auth-

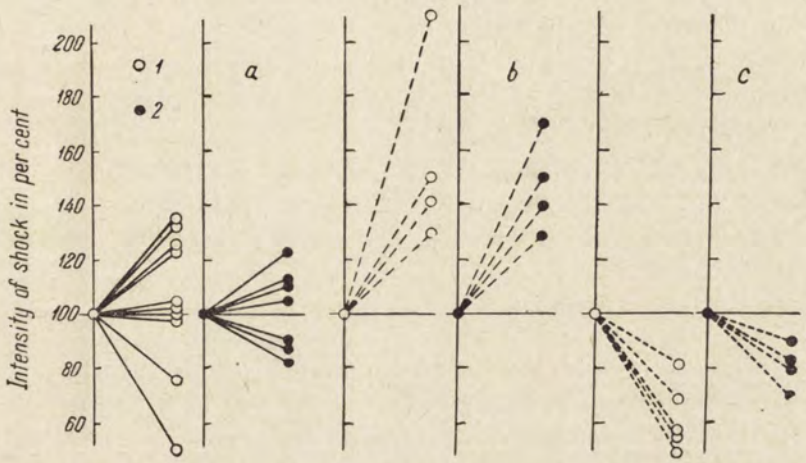

Fig. 6. Changes in threshold of unconditioned defensive response during the experimental session. 100% corresponds to the threshold intensity monitored before each session. Each line represents the change of threshold during one session. 1, dog Dick; 2, dog Puppy. a, data from the experiment with the alternative pairing of the electric shock and food; b, results obtained when electric shock is systematically presented before the food; c, results obtained when electric shock is systematically presented after the food. From the experiment of Varga

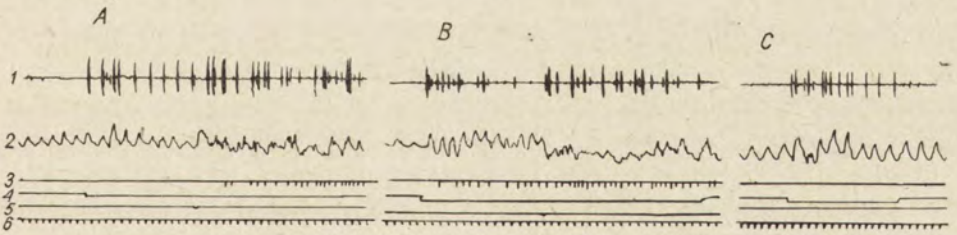

Fig. 7. Changes of the adequate unconditioned reflex of the signalling stimulus during acquisition and extinction of the conditioned food reflex to the air-puff into the eye. A, intensive blinking before the acquisition of the food CR. B, after establishing the food CR the blinking is partially inhibited. C, recovery of the blinking response after the extinction of the conditioned food reflex. Other explanations as in Fig. 2. From the experiment of Rudenko

ors (Gershuni 1947, Giurdzhian 1954) that the afferent cells increase their excitability when the stimulus becomes a conditioned signal. Of course, the other possibility of inhibition being located in the efferent neurons of the UR arc of the signalling stimulus is ruled out.

As seen from what was written above, we adhere to Pavlov's idea of the direct relation of the inhibitory induction, i.e., external inhibition, to the mechanism of the formation of the CR. However, we locate this inhibition in the interneurons of the unconditioned reflex arc of the CS instead of the afferent neurons as Pavlov thought.

It is worth mentioning that, when the CR is subjected to extinction, the adequate UR elicited by the signalling stimulus reapears and becomes strengthened (B in Fig. 7).

From those and other facts we can conclude that there exist reciprocal inhibitory relations between the intermediary links of these two reflex, i.e., a CR and an adequate UR — both elicited by the same stimulus so that their reflex arcs possess a common afferent link. Those mutually inhibiting elements are denoted in Fig. 3 as synapses 1 and 2.

This is a general formula which, of course, may have some exceptions. In some way it resembles the Sherringtonian scheme of interrelations between the flexor and extensor reflexes; the arcs of both reflexes start off the different collaterals of the same afferent neuron so that one could speak of an "initial common link".

Theorizing of this sort also finds support in the experiments on conditioned reflexes occurring due to the backward conditioned connection. It was found that the application alone of the second from a pair of stimuli, i.e., without its usually preceding partner-stimulus, elicits along with the adequate unconditioned response also the response normally evoked by the first, now missing stimulus (Fig. 1 and 2). This reaction is effected through the backward conditioned connection. It can be concluded also that since neither the cortical point of the first stimulus nor the forward conditioned connection are activated, there is no inductive inhibition of the intermediate link of the reflex arc of this stimulus; therefore it is possible that the conditioned reflexsive excitation reaches this link as well as the more efferent neurones of that reflex arc. Furthermore, it has been observed in Pavlov's, Konorski's, Asratian's and other laboratories that the alimentary motor instrumental responses to situation or to some other secondary conditioned stimuli, are inhibited by the food reinforcement, but they often tend to reappear, even with increased intensity, after eating is finished. Here we obviously encounter the well known neurophysiological phenomenon of rebound, i.e., enhanced excitation of the inhibited structures immediately after the removal of the inhibiting factor. Finally, the notion of antagonistic relations bet-

ween reflexes possessing a common afferent link is supported by the following data from our laboratory. If the same CS elicits a conditioned alimentary response in one experimental situation and a defensive CR in another, then the extinction of one of them brings about the appearance of the other CR, that is, a response inadequate for the given situation (experiments of Struchkov).

These and other facts enable us to propose the following mechanism of the development of internal inhibition due to the omission of reinforcement. (i) The reinforcement, i.e., intensive excitation of the center of UR causes the inductive inhibition of the middle link of the arc of the UR to the signalling CS (synapse 2 in Fig. 3), whereas the receiving afferent cells and the elements of the conditioned connection remain uninhibited and ready for action. This view is supported, apart from the above mentioned facts, by the finding of Khodorov and Asratian, that presenting the CS on the background of the already acting US accomplishes a further increase of the unconditioned response. (ii) After the termination of the reinforcing US and the concomitant drop of excitatory processes within its centers the inhibitory effect exerted upon the intermediary link of the proper reflex arc of the CS comes to an abrupt end. (iii) Henceforth, there develops in this link a state of postinhibitory exaltation, a rebound, which, in its turn, inhibits by negative induction the conditioned connection and particularly its initial elements (synapse 1 in Fig. 3). This view is confirmed by our old observation that the CS administered immediately after the termination of the defensive US, or even a short time later, is incapable of eliciting the CR or the elicited response is extremely weak.

Thus, according to our concept, *the inductive inhibition of the elements of the conditioned connection occurs not during the action of the reinforcing UR and is not caused directly by the excitation of the US center, but develops only after the US termination and is mediated by the successive excitatory exaltation of the middle link of the proper reflex arc of the CS*; this exaltation is caused by the termination of inductive inhibition which occurred in this middle link during the UR. This secondarily aroused inhibition within the conditioned connection itself cuts short the trace excitation of the cells constituting the conditioned connection and thus averts the threatening imminent fatigue and exhaustion which would have caused the development of internal inhihition in these cells. On the contrary, nonreinforcement brings about the complete disruption of this two-stage process. The lack of any strong excitation in the UR center and pari passu the lack of inductive inhibition in the middle link of the proper reflex arc of the CS means that there are no prerequisites for the postinhibitory exalta-

tion within this middle link and consecutively the neurons of the conditioned connection remain uninhibited and exposed to the long-lasting trace excitation. If this happens repetitively, as is necessary for establishing internal inhibition, the additive effects of those excitatory processes in the cells of the conditioned connection cause an increasing fatigue and exhaustion which leads to the development of internal inhibition. This inhibitory process has a protective and restorative character and acquires later a coordinative and "economical" significance.

These are the processes which, as we believe, are crucial for understanding those mechanism of development and localization of conditioned inhibition. It is possible, of course, that some others factors also contribute in this entire process, and among other, the factors considered as most important by other authors.

Evidently, our approach corresponds to the same level of theorizing as that of Pavlov, Sherrington (1906) and other classic of neurophysiologists. The scheme of the two-way conditioned reflex arc with its different neurons and synapses, and inferences on the changes in functional state that occur in these cells are constructed in the same spirit as was done in classical neurophysiology where the content of the "black box" was analysed by studying input and output events.

We are perfectly aware that the intimate mechanism of the development of inhibition in the exhausted neurons remains still unknown but this problem belongs to a different level of life sciences, namely, to the physicochemical and biochemical research of the minute structural and functional shifts in neurons, synapses and their components during the excitatory processes. In respect to the lower parts of the central nervous system contemporary neurophysiology, armed with ultra-microelectrodes, cytochemical methods and electronmicroscopy, has achieved remarkable successes on that level. First of all we would like to stress the importance of the discovery of pre- and postsynaptic inhibition as well as their physicochemical and biochemical bases. We think, however, that employing this knowledge in order to explain in more detail the mechanism of internal inhibition, would be of too speculative a character. Moreover, we consider as premature, relying on the less abundant data provided by the above mentioned modern tools of neurophysiology applied directly to the higher portions of the CNS. Nevertheless, we would like to stress the following. No matter how incomplete and debatable are the results of these neurophysiological studies still, they bring a promise and hope for the crossing the demarcation lines between the different levels of experiment on the problem of inhibition in higher nervous activity, fulfilling thus the foresight of Pavlov.

For the time being, even within the frame of the approach selected

by us, we must content ourselves with the hypothetical explanations such as those presented above.

The last point we would like to comment upon is the following. Pavlov used to say that inhibition in the cortical cells is elicited either by the *weak*, or *novel*, or *very strong* stimuli. It does not seem possible to assume that in each of these three cases the same mechanism is in operation. Very strong stimuli result in supralimit inhibition. But how the weak or moderate stimuli even of long duration, cause the supralimit inhibition remains unclear. The more so, that internal inhibition to weak stimuli is trained, as known from laboratory every-day experience, more readily than to strong stimuli. Therefore, we incline to the idea that the formation of internal inhibition belongs rather to *the category of inhibition generated by weak stimuli.* This inhibition is not caused by stimuli directly, but owing to the fatigue and exhaustion produced by prolonged and repetitive excitation of moderate intensity. As a consequence the cells become less labile and excitable and the stimuli become, owing to the elevated threshold of the cells, physiologically weaker and weaker; a specific process of "weakening" of conditioned stimuli takes place. This formulation leaves but little justification for calling the inhibition occurring in such conditions a "supralimit inhibition".

In such a way we outline our extension of Pavlov's ideas on the mechanism of internal inhibition stressing its fit with the new facts and observations. We are hardly convinced, of course, that our concept satisfactorily copes with all the aspects of this "accursed" problem. We could also, after Pavlov, point at the extreme complexity of the problem and admit that our theory does not and could not possibly cover all the available experimental data. We do believe, nevertheless, that our concept, by saving all the basic ideas of Pavlov although shifting the stress from the events occurring in the afferent cells of the CS towards the neurons of the conditioned connection itself, that this concept fits better with the majority of the old and more recently obtained experimental evidence. Moreover, the theory is reformulated in terms which should make it closer to one of the fundamental problems of current neurophysiology, namely, the kaleidoscopic interplay of excitatory and inhibitory processes which occurs in afferent neurons through manifold synaptic contacts with the interneurons of various reflex arcs.

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Editorial note. The article was translated from Russian by Docent S. Sołtysik.

Acta Biol. Exp. 1969, 29: 293—318

Lecture delivered at the scientific session held in commemoration of the 50th anniversary of the Nencki Institute

December 1968

STUDIES ON THE NATURE OF RECENT MEMORY

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There has been a great deal of experimental work and theoretical discussion on the possible mechanism involved in memory processes. A recurrent theme which stems from a paper by Müller and Pilzecker (1900) and was subsequently developed by Young (1938), Hilgard and Marquis (1940), Hebb (1949), Gerard (1955) and Konorski (1967) has been the concept of a period of reverberatory neuronal activity which outlasts the stimulus and preserves information in a dynamic form.

Support for the existance of self-reexciting neuronal circuits has been obtained from the work of Lorente de No (1938) and the electrophysiological studies of Burns (1954) and Verzeano and Negishi (1960). The reverberatory activity is believed to lead to a more permanent form of static engram which depends upon chemical or structural changes. Many hypotheses have been put forward regarding the nature of the process responsible for "long term" memory and an anatomical concept put forward as early as 1893 by Tanzi, that some structural change took place at the neuronal surface, has been developed by Eccles (1953, 1965) in the light of recent knowledge of synaptic function. In addition to anatomical hypotheses, several workers have proposed detailed suggestions involving intraneuronal chemical changes (Monne 1948, Katz and Halstead 1950) including more recently Hyden (1960) whose ribonucleic acid hypothesis has led to a large amount of experimental work.

The transition between the initial phase of reverberatory activity and

the long term "static" registration mechanism is believed to occur by means of a process termed "consolidation". This process has been deduced from the fact that certain interfering agents, of which electroconvulsive shock is the most commonly used, can disrupt the memory mechanism if applied shortly after the information has been registered but are ineffective if applied later. Estimates of consolidation time vary with the species used and behavioural task employed and range from about 10 sec (Chorover and Schiller 1965) to several days (Pearlman et al. 1961). It is usually assumed that the interfering agents, when applied soon after the learning trial, are disrupting reverberatory neuronal activity but it is also possible that they are able to disrupt unstable chemical forms of memory registration. There is an extensive literature concerned with the experimental evidence and theoretical interpretation of the early phases of memory and several recent reviews are available (Gomulicki 1953, Glickman 1961, Deutsch 1962, McGaugh and Petrinovitch 1965, Weissman 1967, and John 1967).

It has also been assumed that there is another form of transient memory which depends upon prolonged perseverative neuronal activity and does not involve consolidation processes (Konorski 1961, 1967). This is a transient memory of perceptions and associations in situations where the subject cannot use his previous experience but has to rely entirely upon recent memory. Several behavioural tasks have been designed to study this form of memory and they invariably involve the display of stimuli and a delay period followed by a response whose correctness depends on remembering the stimulus presented before the delay. The most commonly used tasks of this nature are — delayed response, delayed alternation and delayed "same versus different pair of stimuli" which was introduced by Konorski (1959). Relatively little experimental work has been carried out on the effectiveness of disruptive agents in impairing this type of memory.

In the experimental work reported here we have attempted to establish whether prolonged perseverative neuronal activity is essential during the early period after a learning trial or during the delay in the delayed response procedure. In the first experiment we investigated the effects of severe cephalic ischaemia, resulting in unconsciousness and temporary flattening of the electroencephalogram (EEG), on the acquisition of the somatic and cardiac components of a classically conditioned defensive reflex (Baldwin and Sołtysik 1965, 1966). This type of memory registration following the learning trial is generally considered to be long lasting. The second experiment was concerned with the effects of cephalic ischaemia or alternatively the intracarotid injection of a rapidly metabolised barbiturate (methohexitone sodium), which also produces isoelec-

tric EEG, on the performance of delayed responses. The brain electrical activity was disrupted during the delay period.

We have used goats as our experimental animals because of the peculiar nature of their cephalic circulation (Andersson and Jewell 1956, Baldwin 1964, 1965). Our experimental approach has been based on the assumption that if the memory process survives the period of isoelectric EEG it cannot depend upon sustained interneuronal reverberatory activity because this is unlikely to survive the period of flattened EEG (Baumgartner et al. 1961). Lack of impairment of the memory process would imply that it was probably registered in some intraneuronal chemical form. Unfortunately, the opposite result, namely, an impairment of learning or performance of our subjects after the acute cerebral ischaemia, would not provide any conclusive evidence. The inferior performance might be interpreted in several ways, of which the impairment of recent memory or consolidation is only one alternative.

THE USE OF GOATS AS EXPERIMENTAL ANIMALS

In the goat, almost the entire brain anterior to the medullary region is supplied by blood from the common carotid arteries (Andersson and Jewell 1956). The basilar artery in this species may be regarded as a branch of the Circle of Willis and flow in it is caudad in direction. The basilar artery continues along the ventral surface of the spinal cord as the ventral spinal artery (Fig. 1).

ARTERIAL ARRANGEMENT IN THE GOAT

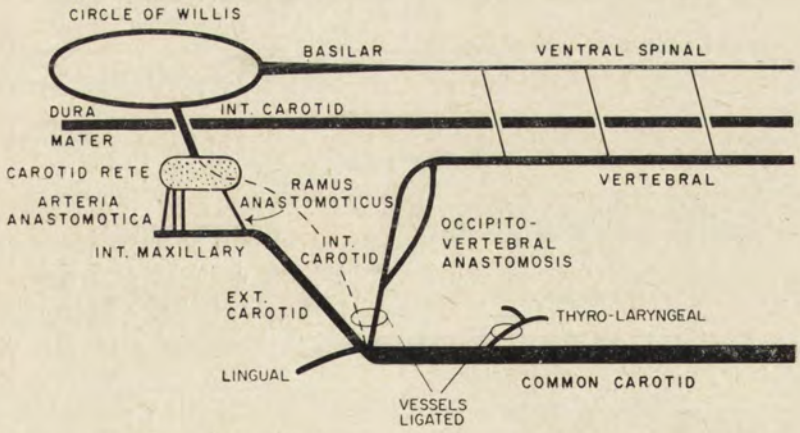


Fig. 1. Diagram showing the arrangement of the cephalic arteries in the goat. The dotted line indicates that the internal carotid artery degenerates in the adult

In most other species the vertebral arteries unite to form the basilar artery and thus supply the posterior portion of the Circle of Willis, but in the goat they terminate at the level of the atlas vertebra and unite with the common carotid arteries via the large occipito-vertebral anastomosis. In their passage up the neck the vertebral arteries give off a number of small branches which join the ventral spinal artery and supply the cervical spinal cord and posterior medullary region.

The goat has a well developed intra-cranial carotid rete through which passes all the blood going to the Circle of Willis. The rete is supplied by vessels derived from the external carotid artery. In adult animals the portion of the internal carotid artery proximal to the rete degenerates leaving only the segment of the artery within the rete from which it emerges to supply the Circle of Willis (Fig. 1).

In the goat, it has been possible to make a chronic preparation in which severe cephalic ischaemia could conveniently and repetitively be produced (Baldwin 1964, Baldwin and Sołtysik 1966). In this preparation both common carotid arteries were exteriorised in skin loops and about one month later the occipito-vertebral anastomoses were bilaterally ligated. This ligation ensured that the only possible source of cephalic blood supply was via the common carotid arteries and cephalic ischaemia could easily be produced by bilateral occlusion of the carotid loops by means of inflatable cuffs. The period during which cephalic ischaemia severe enough to cause flattening of the EEG record could be obtained depended upon the rate at which collateral blood vessels developed and varied from a few days to about three weeks. In order to record EEG conveniently the goats were provided with cranial implants connected to electrodes placed on the cortex and in various subcortical sites.

CLINICAL AND EEG EFFECTS OF CEPHALIC ISCHAEMIA

A few seconds after clamping both carotid loops the EEG frequently displayed low amplitude fast activity but after 8—10 sec large amplitude (> 100 μV) slow waves (3—5 c/sec) appeared in the record and at this time the goat fell unconscious. After 25—45 sec the large amplitude activity diminished and the EEG in both cortical and subcortical regions became isoelectric (Fig. 2). Isoelectric records have been obtained from the caudate region, thalamus and hypothalamus and the rostral mesencephalic reticular formation.

Shortly after falling unconscious the goats exhibited increased muscular tone with arching back of the neck and a rigid extension of the limbs, the whole syndrome resembling decerebrate rigidity. The rigidity was soon followed by a period of flaccidity which often, but not inva-

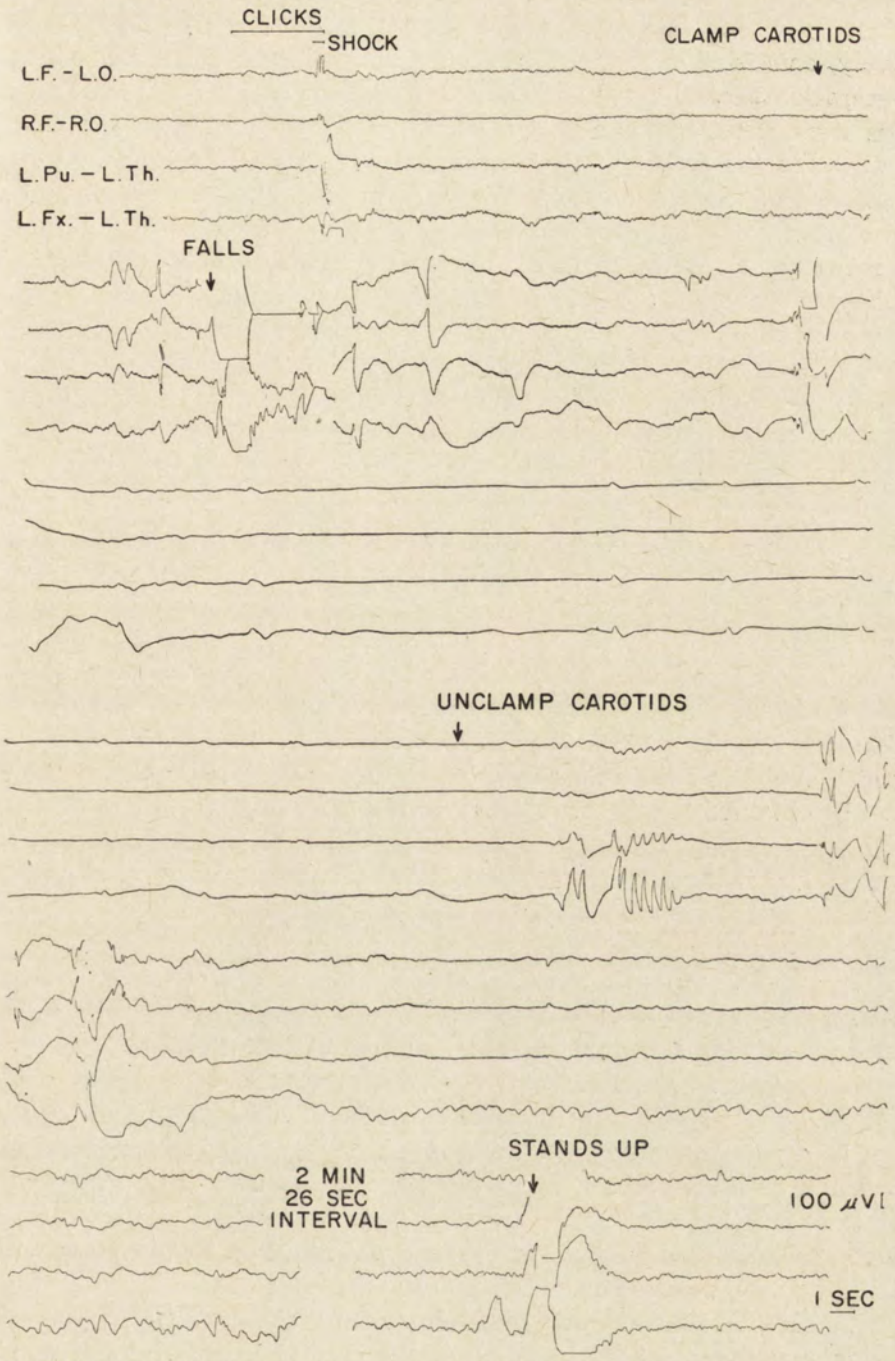


Fig. 2. EEG record showing a typical classical conditioning trial followed by cephalic ischaemia. L. F., Left frontal cortex; L. O., Left occipital cortex; R. F., Right frontal cortex; R. O., Right occipital cortex; L. Pu., Left putamen; L. Th., Left thalamus; L. Fx., Left fornix. Reprinted from Baldwin and Sołtysik 1966

riably, coincided with the appearance of isoelectric EEG. In some cases respiration became irregular and the palpebral reflex was lost. The carotids were clamped for a period of one and a half minutes and then released and the EEG usually reappeared within a few seconds. At first it consisted of large amplitude low frequency activity in cortical and subcortical regions but this changed to a normal EEG record within 1—3 min (Fig. 2). Within a few seconds of the release of the carotids there followed a sudden increase in muscular tone with downward arching of the neck and extension of the limbs. The goats usually recovered rapidly after restoration of the cephalic circulation and were able to stand 3—5 min after removal of the carotid occlusion. On recovery they did not show signs of fear or pain and would often take food from the experimenter.

The time during which the preparation could be used to produce isoelectric EEG not only depended upon the rate at which collateral blood vessels developed but also on physiological factors. It has been demonstrated in sheep that hypertension develops during cephalic ischaemia and this would tend to force blood in an anterior direction along the ventral spinal artery and into the basilar artery. The hypertension would also cause a greater flow through any collateral vessels which had developed (Baldwin and Bell 1963a). In our experience the post operative period in which cephalic ischaemia severe enough to cause flattening of the EEG can be obtained is subject to considerable individual variation.

CLINICAL AND EEG EFFECTS FOLLOWING INTRACAROTID INJECTION OF METHOHEXITONE

In order to obtain a more reliable method of producing an isoelectric EEG record we have developed a technique for the intracarotid injection of methohexitone sodium, a short acting barbiturate which is rapidly broken down in the liver and does not enter the body fat stores. The technique was similar to that used for intracarotid injection of barbiturates in a previous study (Baldwin et al. 1967). In the goat, intracarotid injection produces a high concentration of the drug in the brain rostrally to the medullary region but because they are large animals with a high blood volume it is possible to produce the required EEG effects without building up a dosage sufficient to prolong recovery.

To facilitate intracarotid injections a short nylon catheter with a rubber stopper was passed into one of the carotid loops, and left in place. Methohexitone was injected as a solution containing 25 mg in 1 ml of water. Injections were made with a Harvard pump usually at a rate of 1.94 ml/min and occasionally at 3.88 ml/min. During injections the oppo-

site loop was occluded to ensure a bilateral distribution of the injected barbiturate (Baldwin and Bell 1963b). The total amount of methohexitone injected was determined by the clinical state of the goat and if the EEG was not isoelectric by the time apnoea developed and the corneal reflex became weak the injection was stopped. The usual dose was 50—75 mg and in all cases where respiration became depressed artificial respiration was applied and oxygen administered by means of a face mask.

After 8—10 sec of injection large amplitude (> 100 μV) low frequency waves appeared in the EEG and a few seconds later the goat became unconscious. The EEG changes are shown in Fig. 3 and it can be seen that while the cortical and hypothalamic records became isoelectric in about 50 sec some activity remained in the rostral mesencephalic reticular formation for 110—115 sec. Methohexitone produced isoelectric EEG in cortical and subcortical regions in 66% of injections. Injections at 1.94 ml/min produced isoelectric records in the range of 50—120 sec while injections at 3.88 ml/min produced isoelectric records in 30—50 sec.

Methohexitone, administered by the above technique did not cause excitement and the goats were often able to stand 4—8 min after the start of the injection. The procedure did not appear to cause pain or induce fear.

Experiment 1

THE EFFECT OF CEPHALIC ISCHAEMIA ON THE ACQUISITION OF A CLASSICALLY CONDITIONED DEFENSIVE REFLEX

These experiments were carried out at the University of California at Los Angeles and a complete account has been published (Baldwin and Sołtysik 1966). A group of goats was subjected to 1.5 min of cephalic ischaemia commencing 20 sec after the pairing of the conditioned stimulus (CS) and unconditioned stimulus (US) in a classical defensive conditioning situation. The CS consisted of clicks from a loudspeaker and the US was a mild electric shock to the left foreleg. The conditioned reflexes recorded were flexion of the left foreleg and acceleration of the heart rate to the CS. An outline of the experiment is presented below.

METHODS

Group A (5 goats. Numbers 1—5 in Fig. 4 and Table I)

Each goat had been prepared with bilateral carotid loops, bilateral ligation of the occipito-vertebral anastomosis and a cranial implant connected to cortical and subcortical electrodes. They were treated as follows:

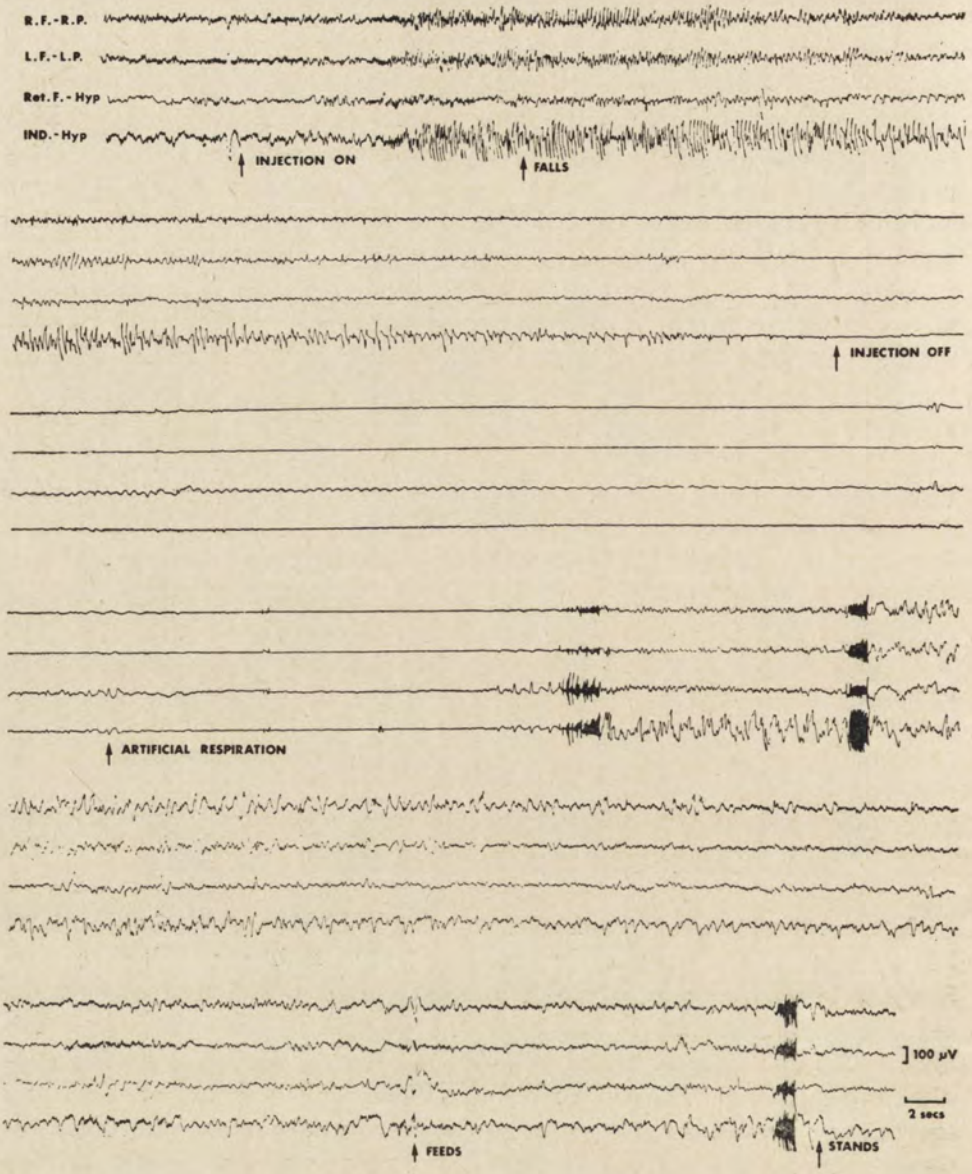
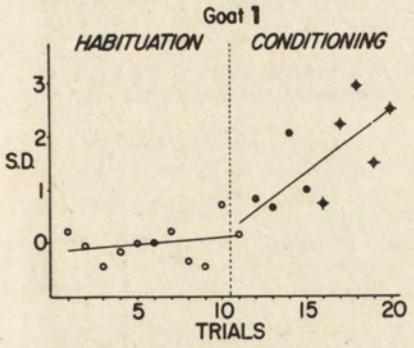
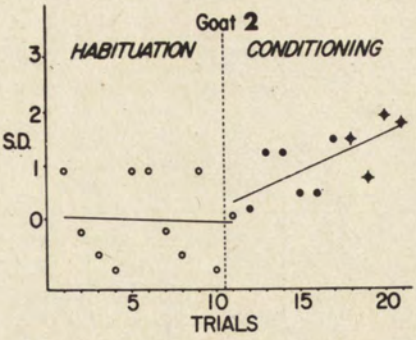
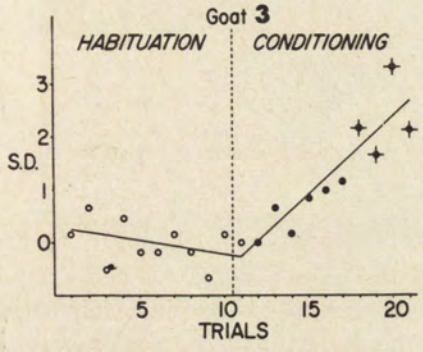


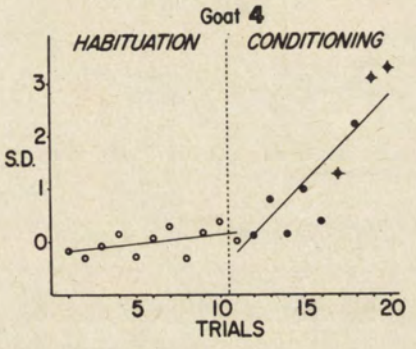
Fig. 3. The effect of intracarotid injection of methohexitone on the EEG. R. F., Right frontal cortex; R. P., Right parietal cortex; Ret F., Reticular formation of the midbrain; Hyp. Hypothalamus; IND., Indifferent electrode. Reprinted from Baldwin and Sołtysik 1969

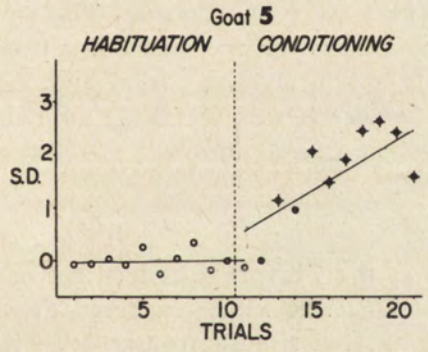
Fig. 4. Acquisition of heart rate conditioned responses in Group A (goats 1 to 5) and Group B (goats 6 and 7). Ordinates: standard deviations calculated for each goat after transformation into Z scores. Abscissae: 10 habituation trials followed by 10 conditioning trials. ⊹ indicates that flexion of the left foreleg took place during the presentation of the CS

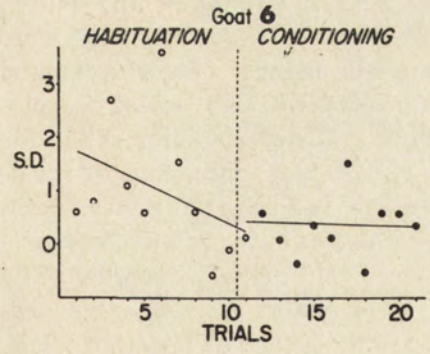












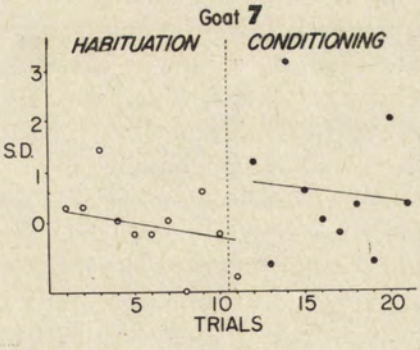


Table I

Rate of acquisition of conditioned leg flexion in experimental and control groups. Criterion was 4 successive leg flexions to the conditioned stimulus[a]

Experimental group A		Control group C	
goat number	trial in which criterion reached	goat number	trial in which criterion reached
1	9	8	13
2	11	9	12
3	10	10	12
4	12	11	9
5	8	12	14

[a] Significance of difference between the groups; by U-test non significant but close to 5% level and by t-test — similarly, $0.05 < P < 0.1$.

HABITUATION

Before starting any conditioning trials the goats were brought to the laboratory each day to accustom them to the experimental conditions. They were restrained on a stand which was inside a sound-attenuating conditioning chamber. On the first day of the experiment the goat received ten presentations of the auditory stimulus from a loudspeaker. The stimulus consisted of clicks at 10 per second and lasted for 4 sec. Ten presentations occurred at irregular intervals during a 1 hr period and the cardiac responses of the goats to the clicks were recorded. All the animals in groups A, B and C were habituated in the above manner.

CONDITIONING

The next day the click stimulus used as the CS was paired with electric shock to the left metacarpus as the US. The shock occurred after 3.5 sec of the CS, lasted 0.5 sec and terminated simultaneously with it. The shock was of 70 v administered from a Grass stimulator and caused a marked flexion of the left foreleg. Movements of the left foreleg were recorded, by means of a strain gauge, on one channel of a six channel Grass polygraph which was also used to record EEG and electrocardiogram (ECG). During the experimental trials one experimenter sat inside the conditioning chamber to occlude the carotid loops by means of pneumatic cuffs. Twenty seconds after the end of the CS—US pairing both loops were rapidly occluded and a one and a half minute period of cephalic ischaemia produced. The EEG and ECG were continuously recorded. The above conditioning procedure followed by cephalic ischaemia was repeated once each day until all the goats had undergone at least ten trials.

The criterion for acquisition of the leg flexion response was 4 high amplitude conditioned leg flexions in 4 consecutive trials.

Group B (2 goats. Numbers 6 and 7 in Fig. 4)

To ascertain whether any component of the cardiac response could be caused by the cephalic ischaemia, two goats were treated as follows. The animals received the same treatment as those in group A except that the shock to the foreleg was omitted i.e., they received 4 sec of clicks as the CS, followed 20 sec later by one and a half minutes of cephalic ischaemia which was serving as a potential US. Recordings were made of EEG, ECG and movements of the left foreleg.

Group C (5 goats. Numbers 8—12 in Table I)

This group of control animals did not undergo any surgical preparation and was subjected to the same conditioning procedure as group A except that cephalic ischaemia was omitted.

Statistical evaluation of the results

To facilitate comparison of the cardiac responses from different goats with different heart rates the results from each goat were converted into Z scores (Edwards 1954). The U-test (Siegel 1956) was used to evaluate the statistical significance between the various experimental groups. Heart rate was calculated from the 10 beats immediately preceding the CS and was compared with the rate estimated from the 5 beats which preceded the onset of the US. In group B in which no shock was given, the rate was estimated from the 5 beats preceding the last 0.5 sec of the CS.

RESULTS

Group A (Goats 1—5 in Fig. 4 and Table I)

This group received the CS—US pairing followed 20 sec later by a 1.5 min period of cephalic ischaemia. As can be seen in Fig. 4 and 5 and in Table I this procedure did not prevent the acquisition of both cardiac and leg flexion conditioned reflexes.

Group B (Goats 6 and 7 in Fig. 4)

These goats were subjected to the CS but not to electric shock. Instead, cephalic ischaemia was produced 20 sec after the termination of the CS. As displayed in Fig. 4 they did not acquire conditioned cardiac reflexes and no conditioned leg flexion developed.

Group C (Goats 8—12 in Table I)

These goats received the CS—US pairing but this was not followed by cephalic ischaemia. As shown in Table I, they all rapidly acquired conditioned leg flexion reflexes and Fig. 5 illustrates the development of cardiac conditioned reflexes in this group.

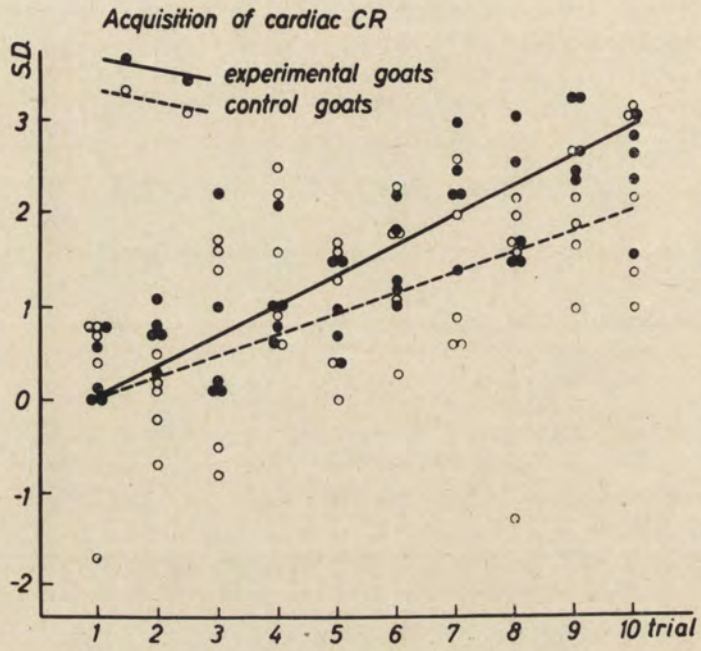


Fig. 5. Acquisition of heart rate conditioned responses in experimental goats (group A) — filled circles, and in control goats (group C) — open circles. Ordinates: standard deviations calculated independently for each goat (transformation into Z scores). Abscissae: first 10 days (trials) of conditioning. Mean response during the 10 habituation trials is arbitrarily taken as 0 level. The regression lines are also shown for both groups: solid line for the group A and broken line for the group C. No significant differences were found between mean conditioned responses and coefficients of regression in both groups, although the experimental group A shows a steeper slope (faster learning) in the presented portion of the acquisition curve. Reprinted from Baldwin and Sołtysik 1966

COMPARISON BETWEEN GROUPS A AND C

1. *Leg flexion* — statistical comparison by means of the U-test did not reveal any statistical differences between the two groups. No statistically significant differences were found between the mean latencies of the conditioned leg flexion reflexes nor between the coefficients of regression calculated for the latencies of the first 5 conditioned responses.

It is worth mentioning, however, that the ischaemia group showed superiority over the controlled group in the rate of acquisition of the leg flexion CR (Table I) and that the difference nearly approached the statistical significance at the 0.5 level.

2. *Cardiac conditioning* — the U-test revealed no significant differences between the two groups with respect to the mean heart rate responses determined from the first 10 conditioning trials. The acquisition curve is somewhat steeper for the experimental group but no significant differences were found between the coefficients of regression calculated for the increase in heart rate responses during the first 10 conditioning trials (Fig. 5).

Experiment 2

THE EFFECT OF CEPHALIC ISCHAEMIA OR THE INTRACAROTID INJECTION OF METHOHEXITONE ON THE PERFORMANCE OF DELAYED RESPONSES IN GOATS

These experiments were carried out during 1967 and 1968 at the A.R.C. Institute of Animal Physiology, Babraham, and they were intended to determine whether a period of disorganised or isoelectric EEG occurring during the delay period would impair performance in delayed response tests. A more detailed account of this experiment will be published elsewhere (*Brain Research* 1969).

METHODS

Eight goats were used and they were prepared with bilateral carotid loops, bilateral ligation of the occipito-vertebral anastomosis and also cranial implants with electrodes in both cortical and subcortical regions. EEG was recorded using a 6 channel Offner polygraph. The delayed response room consisted of a wooden hut about 36 m^2 (Fig. 6) and contained three remotely operated feeders above which devices for presenting auditory and visual stimuli were placed. Before starting the experiments with ischaemia or methohexitone the goats were trained in all the delayed response tests used.

BEHAVIORAL TESTS USED AND THE RESULTS OBTAINED

1. *Double pre-delay response and reward design — effects of ischaemia or methohexitone*

The goat was restrained at the entrance to the delayed response (DR) room at position 1 (Fig. 6) and after drawing back the canvas screen (B in Fig. 6) which prevented the goat looking into the delayed response

room, the animal's attention was attracted to one of the feeders by moving the feeding bowl by means of a nylon line. When the goat was looking at the feeder the compound stimulus was presented for 8—10 sec.

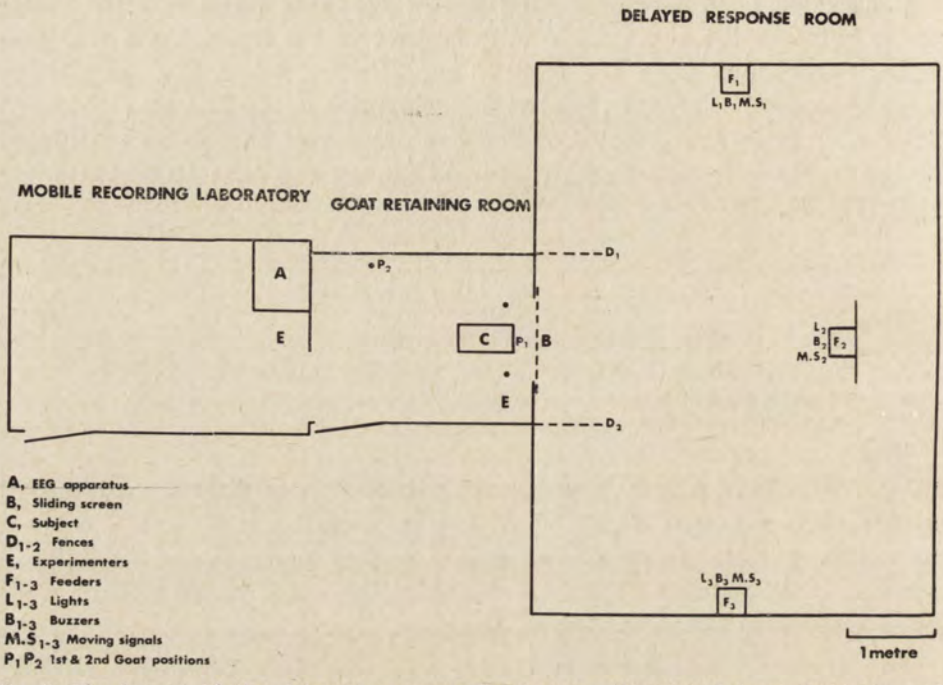


Fig. 6. The layout of the delayed response laboratory. Reprinted from Baldwin and Sołtysik 1969

This consisted of a buzzer, a flashing light and a moving signal arm, all in synchrony at a rate of one per second. The choice of which of the three feeders was used in each trial was determined randomly except that all three feeders were used an equal number of times in each series of 12 or 15 trials and it was arranged that one of the feeders was always used twice in succession during the series of trials. This was to obviate the possibility that the goats might learn not to approach the same feeder on successive trials.

A few seconds after the end of the compound stimulus the goat was released and if it approached within 50 cm of the correct feeder, without first going to the other feeders, it was rewarded with goat nuts delivered remotely by the experimenter. If the goat went first to one of the incorrect feeders no reward was given. After returning from the correct feeder the goat was restrained in position 2 (Fig. 6) and the canvas screen drawn across to prevent the goat looking into the DR room. One of the

experimenters then entered the delayed response room and refilled the food dispenser taking care to avoid leaving olfactory cues by visiting all the feeders. This procedure took 30—45 sec. When the experimenter returned after filling the food dispenser, the canvas screen was drawn back and the goat released without a signal being given. If it went to the correct feeder the goat was rewarded with food and after eating it voluntarily returned to the starting place. At this point the 10 min delay period began and the goat was restrained in position 2 (Fig. 6) and the canvas screen drawn across the entrance to the DR room. During the delay period either cephalic ischaemia was produced or methohexitone administered. While the goat was unconscious the feeder was refilled and care was again taken as before to avoid olfactory cues. When the goat had recovered it was restrained in position 1 (Fig. 6) and at the and of the 10 min delay period the canvas screen was drawn back and the goat released to make its choice. If it went to the correct feeder it was rewarded. Two trials were given each day one in the morning and the other in the afternoon.

Results

The results of the trials in which cerebral ischaemia was produced are shown in Fig. 7 and it is apparent that the goats were usually able to make the correct choice even in those trials in which the EEG became isoelectric. The development of collateral blood vessels reduced the number of isoelectric trials except in goat 36.

The results obtained when methohexitone was injected during the delay period are displayed in Fig. 8 and it is clear that it did not seriously impair the performance of the goats.

2. *Pre-delay response design — effects of ischaemia or methohexitone*

The goat was initially restrained in position 1 (Fig. 6) with the canvas screen drawn back so that it could see into the DR room. The same compound stimulus as used previously was presented, beginning with the movement of the feeding bowl. The goat was released a few seconds after the end of the stimulus and if it went to the correct feeder a "symbolic" reward consisting of a short metal chain was dropped into the feeding bowl from the food dispenser. The goats usually examined the chain and sometimes tried to chew it before returning to the starting position. As soon as the goat had returned to the starting place the 10 min delay period began and during this period ischaemia was produced or methohexitone administered. While the goat was unconscious one of the experimenters removed the chain and refilled the food dispenser with goat nuts. All the feeders were visited and refilled to avoid leaving any

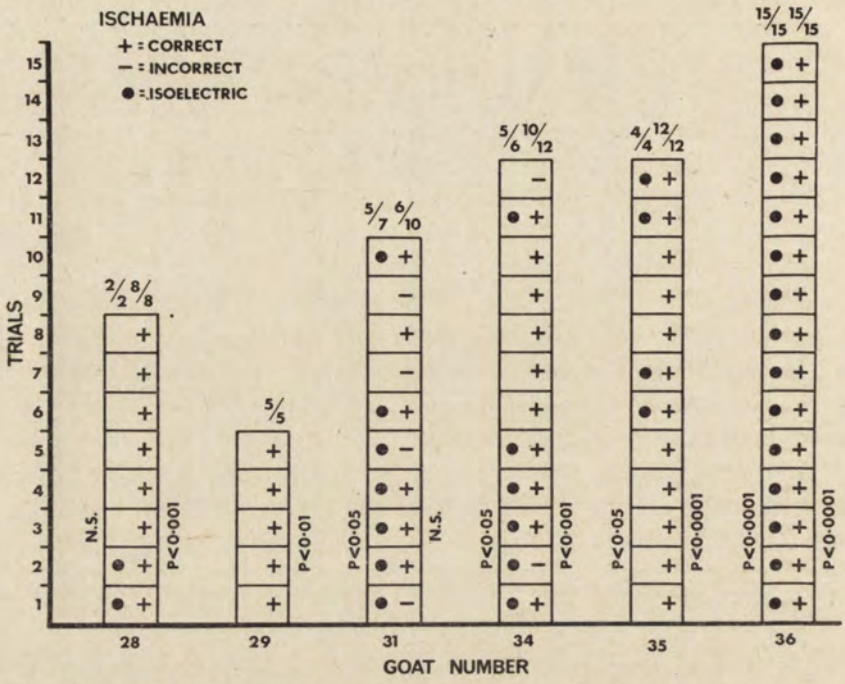


Fig. 7. Double pre-delay response and reward design. Effects of cephalic ischaemia. Statistical significance determined using the Binomial test. With three feeders the chance expectation is 1/3 correct. The P-values on the left of the columns refer to the isoelectric trials. The P-values on the right of the columns refer to all the trials. The fraction at the top of each column on the left refers to:

$$\frac{\text{isoelectric trials with correct choice}}{\text{all isoelectric trials}}$$

and the fraction at the top of the column on the right refers to: $\frac{\text{correct choice trials}}{\text{all trials}}$

scent cues. When the goat had recovered it was restrained in position 1 and at the end of the 10 min delay period the canvas screen was drawn back and the goat released. If it went directly to the correct feeder it received a reward of goat nuts. Two trials were carried out each day, one in the morning and the other in the afternoon.

Results

When used in this test the goats had begun to develop collateral blood vessels and cephalic ischaemia severe enough to produce an isoelectric EEG was not often obtained. The results of the trials in which ischaemia was produced are illustrated in Fig. 9 and it can be seen that goats 35 and 36 performed successfully. Only a limited number of ischaemia trials took place because the goats did not always become deeply unconscious and it was considered possible that mild cephalic ischaemia might be aversive.

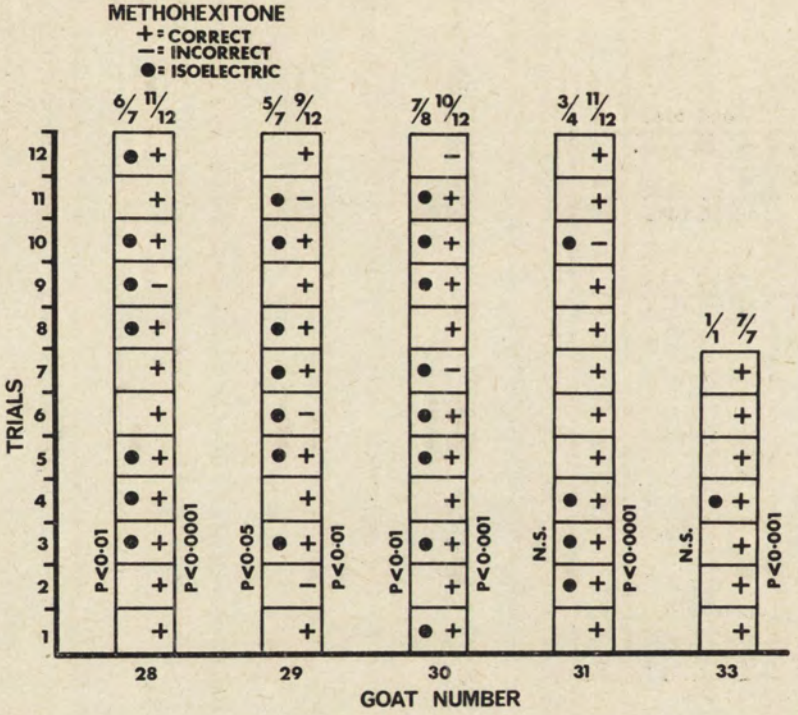


Fig. 8. Double pre-delay response and reward design. Effects of intracarotid injection of methohexitone. Explanations as in Fig. 7

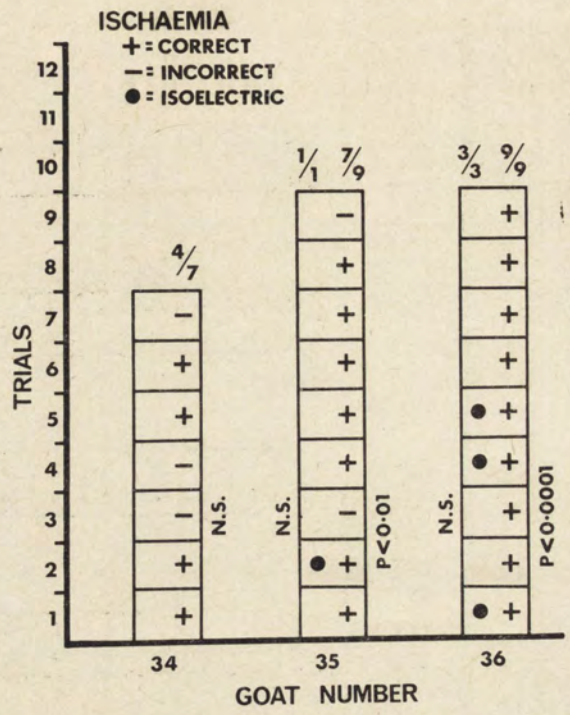


Fig. 9. Pre-delay response design. Effects of cephalic ischaemia. Other explanations as in Fig. 7

The results obtained when methohexitone was administered are shown in Fig. 10 and it can be seen that with the exception of goat 28 all the animals usually performed successfully even in the isoelectric trials.

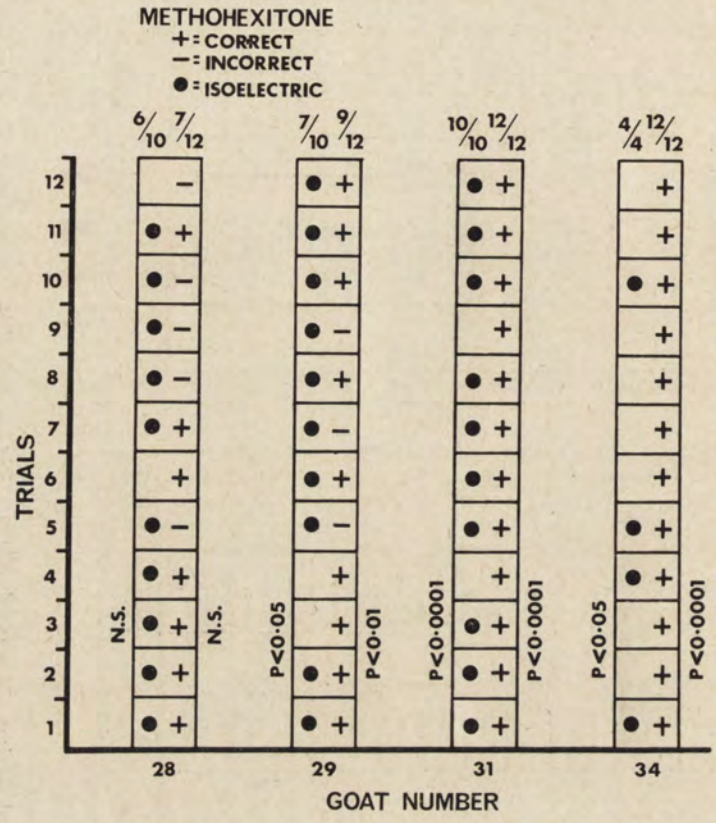


Fig. 10. Pre-delay response design. Effects of intracarotid injection of methohexitone

3. *Delayed response to the stimulus only (i.e., post-delay response and reward design) — effect of methohexitone*

The goat was restrained in position 1 (Fig. 6), the canvas screen drawn back and the compound stimulus applied for about 10 sec. At the end of the stimulus the experimenter remotely delivered food into the feeding bowl while the goat watched. The screen was then drawn accross the entrance to the delayed response room and the 8—10 min delay period began during which methohexitone was administered. While the goat was unconscious one of the experimenters refilled the food dispenser and visited the other feeders. When the animal had recovered from the methohexitone it was restrained in position 1 and after drawing back the

canvas screen it was released. The delay periods ranged from 8—10 min and if the goat went to the correct feeder it was rewarded with food.

Results

The results obtained in the three goats which were tested are illustrated in Fig. 11. These animals had only been trained using delays of up to 5 min but, despite this, goat 30 was able to perform successfully even in trials in which isoelectric EEG was produced.

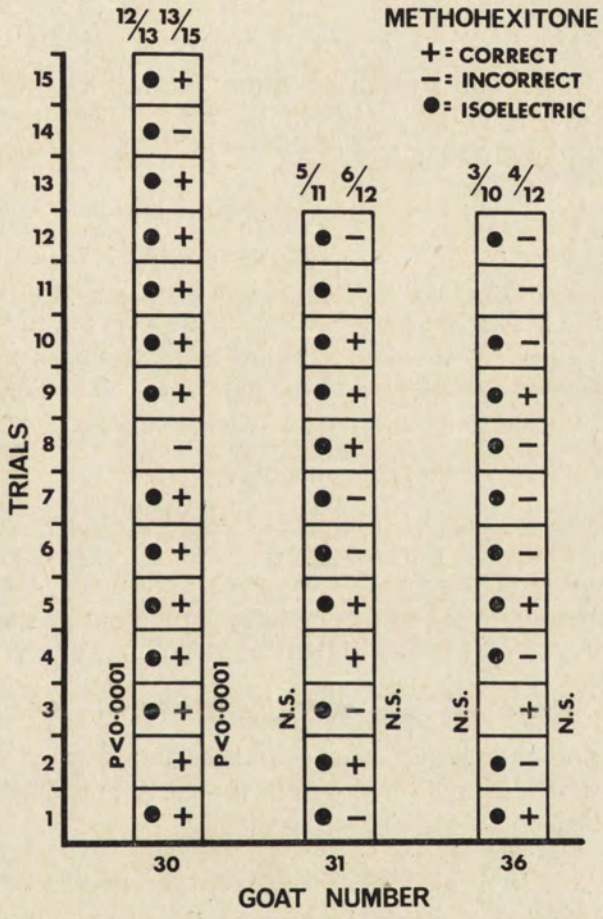


Fig. 11. Delayed response to the stimulus only. Effects of intracarotid injection of methohexitone

BEHAVIOURAL TESTS USING LONG DELAYS DURING WHICH BRAIN ELECTRICAL ACTIVITY WAS NOT DISRUPTED

In these tests no cephalic ischaemia was produced and no methohexitone administered. The long delay tests were applied to ascertain if the successful performance could not be based on a "one-trial learning" phe-

nomenon, especially using design which involved the rewarded response before the delay period. If it is learning, the performance should not deteriorate with the passage of time.

1. *Double pre-delay response and reward design — 10 min delay*

The delay was 10 min and after 2 min initial restraint in position 2 (Fig. 6) the goats were walked around outside the DR laboratory before being restrained again to complete the 10 min delay period.

2. *Double pre-delay response and reward design — 1 hr delay*

After spending 2 min restrained in position 2 the goats spent the remainder of the 1 hr delay period in their pens. Two tests were given each day one in the morning and the other in the late afternoon.

3. *Double pre-delay response and reward design — 24 hr delay*

These tests were conducted as follows: on day 1 the signal was given and the goat made the two initial responses after which it was restrained in position 2 for 2 min before returning to its pen for the remainder of the 24 hr delay period. On day 2, 24 hr later, the goat was tested. On day 3 the next signal was given and the pair of initial responses took place and the goat returned to its pen. 15 trials were carried out in 30 days.

Results of the above tests

The results of the tests using delays of 10 min, 1 hr and 24 hr are illustrated in Fig. 12 from which it can be seen that after 10 min delay all the goats performed successfully, after 1 hr delay 4 out of 5 goats were successful while after 24 hour's delay only 2 out of the 5 goats were able to make the correct choice a significant number of times.

4. *Pre-delay response design — 10 min delay*

The delay period followed after the initial unrewarded response. Two trials were carried out each day, one in the early morning and the other in the late afternoon.

5. *Pre-delay response design — 1 hr delay*

Immediately after the initial response the goat was restrained for 2 min in position 2 (Fig. 6) and after this was returned to its pen for the rest of the 1 hr period. Two trials were carried out each day, one in the early morning and the other in the late afternoon.

Results of the above tests

The results obtained are displayed in Fig. 13 and it can be seen that although all the goats performed well after delays of 10 min none of

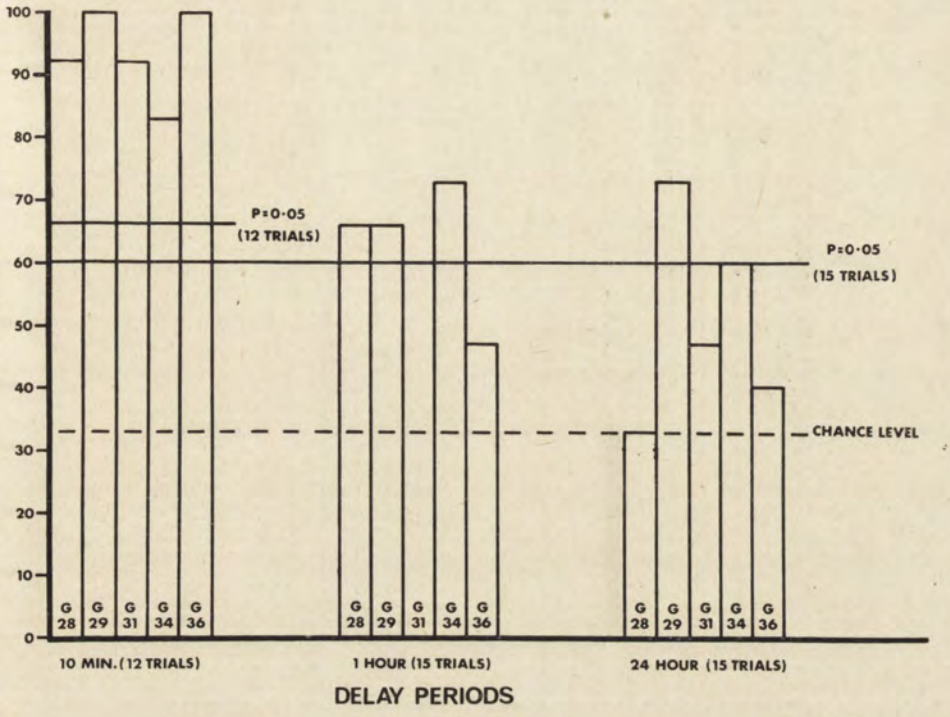


Fig. 12. Double pre-delay response and reward design. Effect of increasing periods of delay. For details see text. Chance expectation of correct choice is 33%. P = 0.05 level of confidence is reached at 66% correct responses using 12 trial block and 60% correct responses using 15 trial block. The goat numbers are indicated at the foot of each column. Reprinted from Baldwin and Sołtysik 1969

them were able to perform significantly above chance level after delays of 1 hr. The results indicate that this test is well suited for the study of short term memory.

DISCUSSION

The results obtained in the first experiment using classical defensive conditioning demonstrated that the goats which received cephalic ischaemia commencing 20 sec after each pairing of the conditioned and unconditioned stimuli acquired both cardiac and somatic conditioned reflexes as rapidly as did the control animals in which ischaemia was not produced (Fig. 5 and Table I). Since the EEG was lost 25—45 sec after the occlusion of the carotid arteries it was apparent that 45—65 sec (adding the 20 sec before clamping) after the pairing of the CS and US unit neuronal activity was lost in the cortical and subcortical regions.

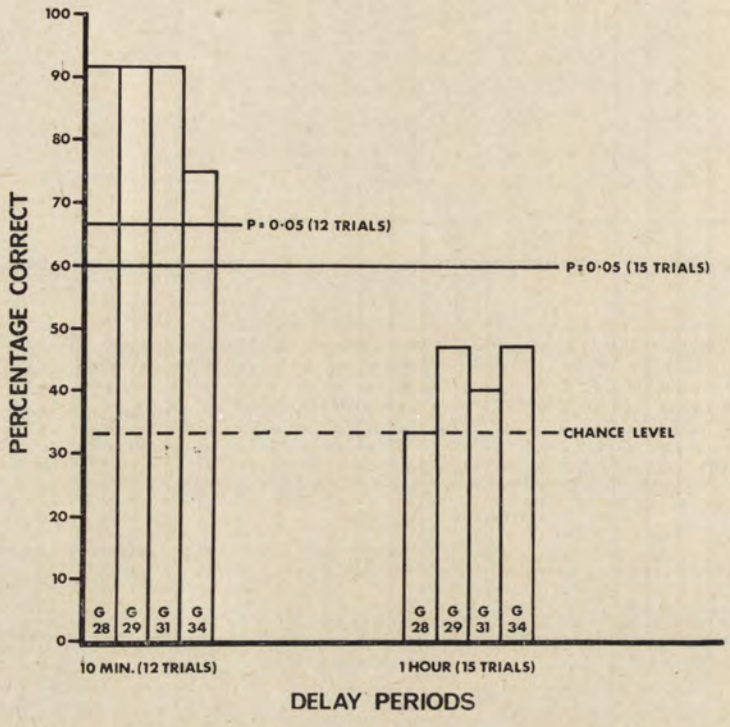


Fig. 13. Pre-delay response design. Effect of increasing periods of delay. For details see text. Other explanations as in Fig. 12. Reprinted from Baldwin and Sołtysik 1969

The experiments in which no electric shock was used and in which cephalic ischaemia was employed as a possible noxious US, revealed that the ischaemia made no contribution to the cardiac conditioning (Fig. 4).

It has been demonstrated by Baumgartner et al. (1961) using cats made anoxic by breathing nitrogen that during the slow waves in the EEG the neurones either cease to discharge or begin to discharge in bursts. During the isoelectric EEG record they found that all unit neuronal activity was absent. Further work is obviously necessary to ascertain whether the same depression of unit activity occurs during ischaemia. It has been established in a limited number of experiments using sheep anaesthetised with a mixture of urethane and chloralose that unit activity disappears during the isoelectric period and returns when the circulation is restored (Baldwin and Sołtysik — unpublished observations). In view of Baumgartner's et al. (1961) results it is most improbable that any unit activity survives during the period in which the EEG is isoelectric. During ischaemia the neurones are not only subjected to shortage

of oxygen but also to a build up of carbon dioxide and other waste products in the nervous tissue.

The perseverative neuronal trace hypothesis would appear to assume a precise spatio-temporal pattern of neuronal activity but even during the initial stage of ischaemia characterised by unconsciousness and large amplitude slow wave activity it is likely that such patterns would be disrupted. If this were so it would suggest consolidation occurred within about 30 sec after each conditioning trial. This idea receives some support from the experiments of Chorover and Schiller (1965) in which electroconvulsive shock was ineffective in producing retrograde amnesia if administered later than 10 sec after the learning event in a "one trial learning" situation using a passive avoidance procedure in rats.

The second series of experiments using the delayed response procedure was intended to test the reverberation hypothesis in a situation where correct performance is based upon short term memory which is not processed into long term memory. The series of tests in which longer delays were used demonstrated that the performance of the goats deteriorated, particularly in the "pre-delay response" design (Fig. 12 and 13). Thus the delayed response tasks used were good tests for short term memory.

The results obtained following the production of cephalic ischaemia or administration of methohexitone during the delay period, indicate that successful performance in delayed response tests does not depend upon prolonged perseverative activity of the brain. Since prolonged reverberation has been eliminated the only feasible hypothesis is that some rapidly induced chemical or structural change occurs in the relevant neuronal pathways to register the information. It is worth pointing out that our results do not invalidate the concept of reverberating activity providing an initial means of registering the memory in a dynamic form but they do rule out the possibility of this process lasting for a prolonged period as the only mechanism of recently acquired memory traces.

SUMMARY

1. Because of the peculiar nature of their cephalic blood supply, goats are particularly suitable animals for the study of the effects of cerebral ischaemia or the intracarotid injection of drugs on memory processes.

2. Two convenient and non-aversive procedures are outlined for disrupting brain electrical activity and producing a temporary period of isoelectric EEG. One depends upon cephalic ischaemia and the other on the intracarotid injection of methohexitone, a rapidly metabolished barbiturate.

3. A period of isoelectric EEG beginning 45—65 sec after the pairing of the CS and US in a classical defensive conditioning situation did not impair the acquisition of cardiac and somatic conditioned reflexes.

4. A period of isoelectric EEG applied during the delay period in three types of delayed response procedures did not significantly impair the successful performance of these tasks which depend upon short term memory.

5. As unit neuronal activity is unlikely to survive during isoelectric EEG it is concluded that prolonged perseverative neuronal activity is not responsible for maintaining the memory trace in the above situations.

We wish to thank Mr J. O. Yates and Mrs Phyllis Albritton for their technical assistance and Mrs V. Mansfield for looking after some of the goats used.

Bibliographic aid was from the UCLA Brain information service which is part of the National Information Network of NINOB and supported under contract PH 436659.

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Acta Biol. Exp. 1969, 29: 319—334

Lecture delivered at the scientific session held in commemoration of the 50th anniversary of the Nencki Institute

December 1968

PROPERTIES OF STRIATAL NEURON-LIKE NETS

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1. INTRODUCTION

One of the major aims of analysing and modelling neural structures it to obtain a verified explanation of the results of neurophysiological investigations. However, many attempts of performing such analysis and construction of models encounter two basic difficulties:

1. The extreme complexity and variety of the structures both studied and simulated.

2. The existing approaches have many loopholes and have to be supplemented with hypotheses.

The difficulties mentioned above make it necessary to introduce thoroughgoing simplifications in the description of neural structures, which provide a relatively simple approach. However, care should be taken not to exaggerate, since otherwise the general and particularly interesting properties of the structure studied may be lost.

In the present report an approach to the description of neural nets is presented which may prove interesting both for neurophysiologists and technicians.

Let us consider a set of neuron-like elements which are arranged in layers and interconnected according to certain simple rules. Each element of this set has properties corresponding to those generally accepted for neurons, namely spatial and time summation of signals from numerous inputs, threshold characteristic, an operational range within which the frequency of generated impulses varies depending on these inputs, and a region of saturation ceiling.

2. CERTAIN PROPERTIES OF TWO-LAYER NETS

We shall now recapitulate certain properties of a set of neuron-like elements which are arranged in two layers (Fig. 1), where every element of the first layer affects (stimulates or inhibits) the action of a certain

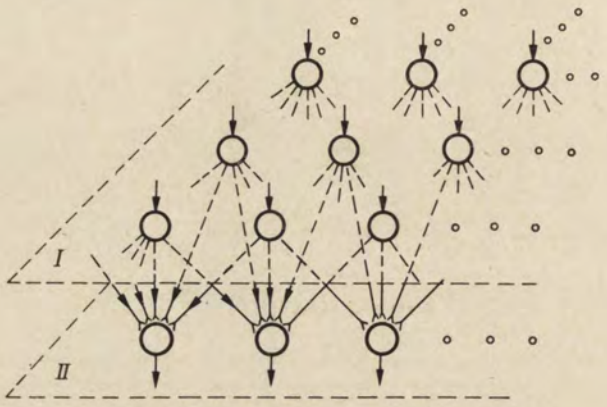

Fig. 1. The structure of a two-layer net

group of neurons in the second layer. This type of net will be referred to as a two-layer net with local connections. Two well known kinds of lateral effects, namely lateral inhibition and lateral excitation, may serve as a simple example.

Let us denote the value of excitation of the first layer by $W(x, y)$ (represented in Fig. 2 in the shape of the letter K). The quantities x and y are the distances along the rectangular co-ordinates. The problem consists in finding the excitation distribution $Y(x, y)$ in the second layer and its dependence on the connection rules assumed. If we section the two-layer net with a vertical plane, we shall obtain a one-dimensional net which we shall refer to as a chain (Fig. 3 and 4). Such nets have been studied extensively by numerous authors (Reichardt and MacGintie 1962, Varju 1962, and Foerster 1964, 1967).

A chain of neurons connected according to lateral inhibition rules is presented in Fig. 3. As is well known, nets of this type are capable of detecting sudden variations in the excitation of the first layer. The second rule quoted — the rule of lateral excitation — is presented in Fig. 4. As may be seen, such nets are capable of detecting gaps in the excitation of the first layer.

However, the properties of a two-dimensional net with a striatal structure are far more interesting. A small section of such a net with divergent and convergent connections is shown in Fig. 5 (where only conver-

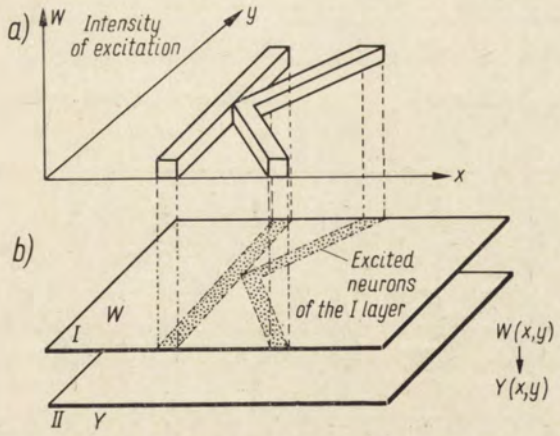

Fig. 2. Transformation of the excitation distribution in a two-layer net. On Fig. 2a an example of an excitation pattern $W(x,y)$ (distribution of excitation) has a shape of letter K. It means that excited neurons which lies in the first layer of the net (Fig. 2b) form the same pattern that is a letter K. As a result of lateral influences among neurons of the first layer and second one, the distribution of excitation of the second layer $Y(x,y)$ may have a quite different from

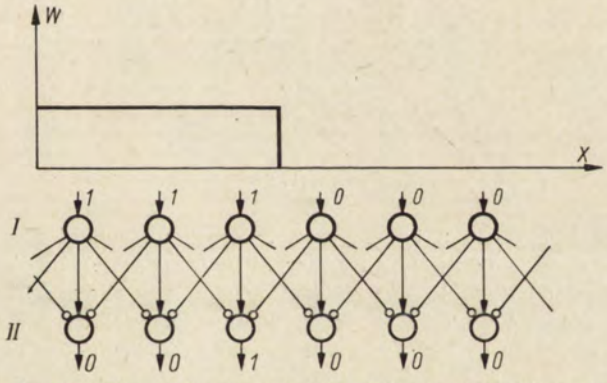

Fig. 3. One-dimensional net with lateral inhibition. Neurons are denoted by big circles. The arrows denote exciting synapses and the small circles — inhibiting synapses

gent connections are shown). Every connection has its own characteristic transmittance which is sometimes referred to as weight. These weights are denoted here as V_{ij}, where the indices i and j are the distances (number of rows and columns, respectively) from the neuron situated above the excited or inhibited neuron. The aforementioned rules of interaction, namely lateral inhibition and lateral excitation, are presented in Fig. 6, where the distance x from the central element is plotted on the abscissa and the weight corresponding to the given distance on the ordinate.

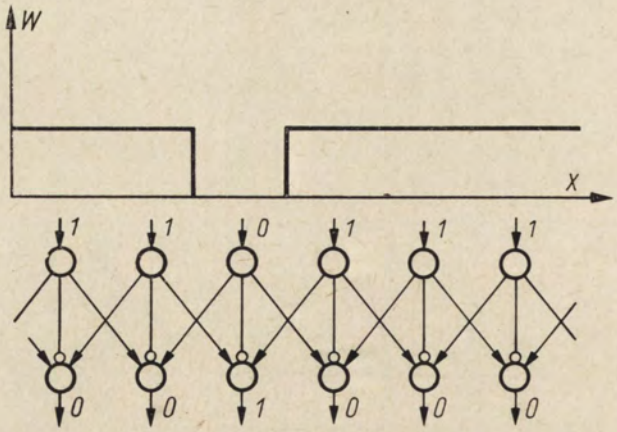

Fig. 4. One-dimensional net with lateral excitation

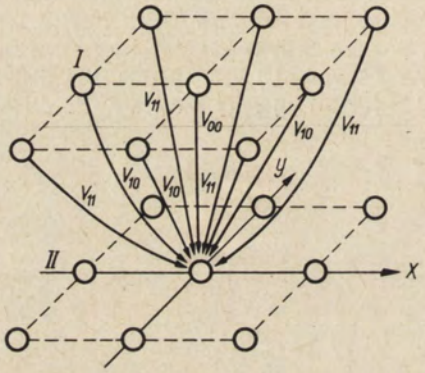

Fig. 5. Rule for linkage in a two-layer net. Every neuron of the second layer is influenced (inhibited or excited) by a group of neurons which lie above that neuron. Here only the connections to one central neuron are shown. The magnitude of that influence depends on corresponding connections values (weights) which are denoted by V_{ik} — where indices i and k denote the distance from the central neuron

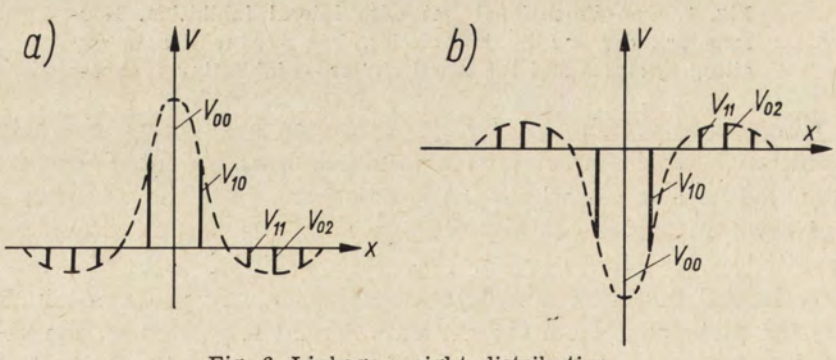

Fig. 6. Linkage weight distribution

It is well known that in two-layer nets with lateral inhibition, the phenomenon of contrast is observed (Fig. 7) (Reichardt and MacGintie 1962, Furman 1965, Gawroński 1967a,b, Gawroński and Zmysłowski 1967). Only those neurons of the second layer are excit which lie on the edge of the excitation distribution of the first layer. As may be seen from Fig. 7

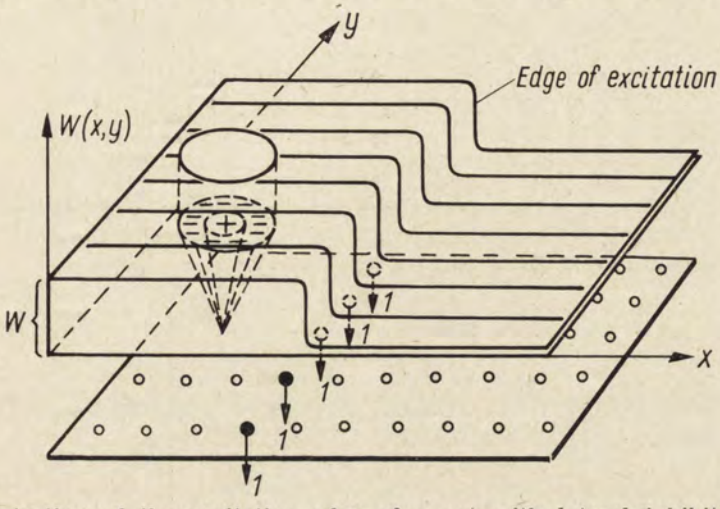

Fig. 7. Detection of the excitation edge of a net with lateral inhibition. In the excited region of the first layer (on the left) the effects from the fields of excitation (+) and inhibition (−) compensate and corresponding neuron from the second layer is not excited. On the edge of excited region the field of inhibition is smaller and corresponding neurons of the second layer are excited

the situation is analogous to that shown in Fig. 3. Every variation in the excitation of the first layer produces a certain assymmetry in the existing excitation-inhibition equilibrium, and hence excitations predominate over inhibitions in the corresponding neurons of layer two.

It appears, however, that the rule of connections considered above has a number of other important features (Dulewicz 1967). Let us consider for a while several letters as examples of simple patterns which are to be recognized (Fig. 8). No doubt the regions of the letter which contain essential information, facilitating the classification, play a significant part in the recognition process. These regions, marked in Fig. 8, 9 and 10 with

Fig. 8. Informative regions (points) for simplified (Roman) letters

dashed circles, are known as informative regions. They determine the position of bends, ramifications, crossings, etc. It was found (Gawroński 1967a, 1968) that informative regions (possibly points) of this type may

Fig. 9. Informative regions of the end and bend type

be divided into two groups. We shall class in the first group all kinds of bends, the end of a line constituting a limit case of a bend (Fig. 9). In the second group we shall class all kinds of ramifications and crossings (Fig. 10).

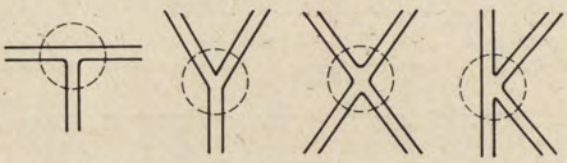

Fig. 10. Informative regions of the crossing type

It may easily be proved by mathematical methods or graphical analysis that two-layer nets with lateral inhibition permit the detection of the informative regions of the first group (Gawroński 1967a, 1968). This may be seen in Fig. 11. If the excitation to inhibition ratio is so adjusted

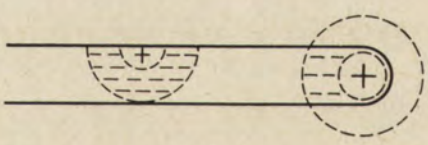

Fig. 11. Graphical interpretation of the rule of detecting the ends in lateral inhibition. Regions of excitation and inhibition for a sector of an enlarged line are shown. On the end of a line the region of inhibition is smaller and corresponding neuron of the second layer is more excited

that for a given straight line (Fig. 11 thick line) the total excitation at most may equal the total inhibition, then of course the corresponding neurons of the second layer will not be excited. However, in the region of bends and even more so at the end of the line a reduction of the in-

hibiting field is observed (Fig. 11). The higher is the resultant increase of excitation in these regions the stronger is the curvature of the line stimulating the first layer. In this way the presence of informative points of the first group may be detected in the pattern. It appears, however, that the rule of connections considered does not allow the detection of informative points of the second group. This may be explained by Fig. 12.

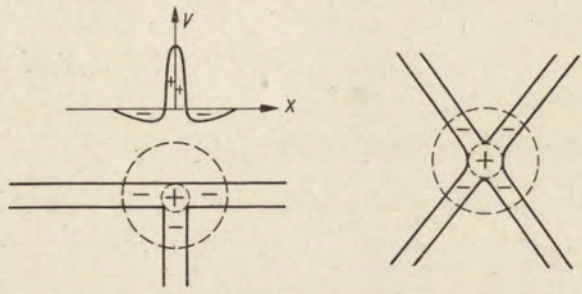

Fig. 12. Graphical interpretation showing that detection of informative regions (points) of crossing type by the lateral inhibition is not possible

The more ramifications a given informative region has the more pronounced is the effect of lateral inhibition. It is necessary therefore to apply in this case the opposite rule, namely the rule of lateral excitation analogous to that presented in Fig. 4 (for the one-dimensional case). As may be seen from Fig. 13, the excitations corresponding to the converging lines sum up in the crossing point.

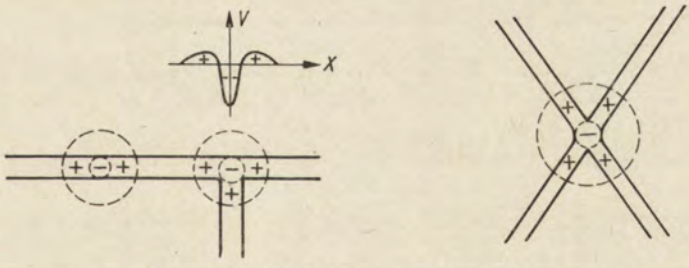

Fig. 13. Detection of crossings by lateral excitation

It follows, therefore, that only a combination of both rules lateral inhibition and lateral excitation — allows us to detect all basic informative points (regions). Using suitable mathematical methods based on the specially adapted matrix calculus, we can calculate the distribution of excitation regions (points) $Y(x, y)$, in the second layer. For this purpose we must know the distribution of excitation regions in the first layer, the

properties of the elements described by the function $f(U_p)$ (where U_p is the resultant excitation of each element), and the distribution of the weights of connections (as denoted in Fig. 5).

Below some mathematical relations are presented to give the reader some general knowledge of the mathematical apparatus which is applied here, and of the possibilities it affords. However, the knowledge of these methods is not necessary for understanding the considerations given in this report.

The final (abbreviated) formula describing the relation $Y(x, y)$ has the form (Gawroński 1968)

$$[Y] = \operatorname{diag}[f]\{[W][V]_o + [W]^T[V]_*\} \tag{1}$$

where $[W]$ and $[Y]$ are matrices whose elements determine the values of the excitation of the first and second layer, respectively, and

$$[V]_* = \sum_{s=1}^{h} {}^{s}_{s}[1][V]_s \tag{2}$$

where

$$ {}^{s}_{s}[1] = \begin{array}{l} \overbrace{}^{s \text{ columns}} \\ \left.\begin{array}{l} \\ \\ \\ \\ \\ \\ \\ \\ \end{array}\right\} k \text{ rows} \end{array} \begin{bmatrix} 0 & 0 & \ldots & 0 & 1 & 0 & \ldots & 0 \\ 0 & 0 & . & & 0 & 1 & 0 & \ldots \\ . & . & . & . & & & & 0 \\ . & & . & . & . & & & 1 \\ 0 & & & . & . & . & . & 0 \\ 1 & 0 & & & & . & . & \vdots \\ 0 & 1 & & & & & . & .0 \\ 0 & 0 & 1 & 0 & \ldots\ldots\ldots & & 0 & .0 \end{bmatrix} \tag{3}$$

The matrix $[V]_s$ characterizing the connections is constructed according to the following rule:

$$[V]_s = \begin{bmatrix} V_{s0} & V_{s1} & V_{s2} & \ldots & V_{sh} & 0 & \ldots & 0 \\ V_{s1} & V_{s0} & V_{s1} & \ldots & & & & \\ . & . & . & & & & & \\ . & . & . & . & & & & \\ . & . & . & . & . & & & \\ V_{sh} & & . & . & . & & & \\ . & & & . & . & . & & \\ . & & & & . & . & . & \\ . & & & & & . & . & V_{s1} \\ 0 & & & & & V_{s1} & & V_{s0} \end{bmatrix} \tag{4}$$

From formula (1) we are able to determine the distribution of excitation and hence the shape of the receptive field of a given neuron which can be compared with the results of physiological experiments. Moreover we can find the weights of the connections (and hence the shape of the receptive field), so as to obtain the selection of a required excitation pattern.

3. ONE-LAYER NETS

Beside the nets with connections between the elements of two layers described above, nets of a different type in which the connections occur between neighbouring elements of the same layer are also possible (Fig. 14). This theoretical possibility may be supported by a number of physiological and morphological premises from which it follows that the probability of structures in which the neighbouring elements are mutually influenced is considerable. Hence, the question arise what are, in general, the possibilities of such structures; are they capable of detecting certain specific excitations (informative regions), and whether two different rules of connections are also necessary here. Below we shall concentrate on

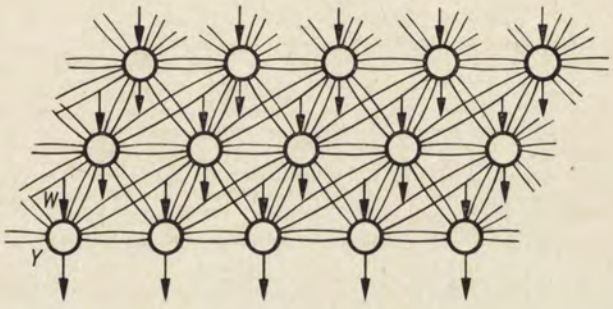

Fig. 14. One-layer net

the comparison of nets with connections between two different layers, and nets with connections in the same layer. This problem was studied by several authors (Reichardt and MacGintie 1962, Varju 1962, Furman 1965, Foerster 1967), and solved for specific cases, mostly for a one-dimensional neuron chain.

Examples of one-dimensional structures (neuron chains) enabling us to compare two-layer nets (a) and one-layer nets (b) are presented in Fig. 15. In these examples lateral inhibition is obtained either through internuncial neurons or through presynaptic inhibition.

The connections between neighbouring elements involve a great number of feedback loops and the possibility of related phenomena occurring.

Above all instability and selfexcitation phenomena are possible, which result from the fact that numerous connections through which the signal may return to the input are available.

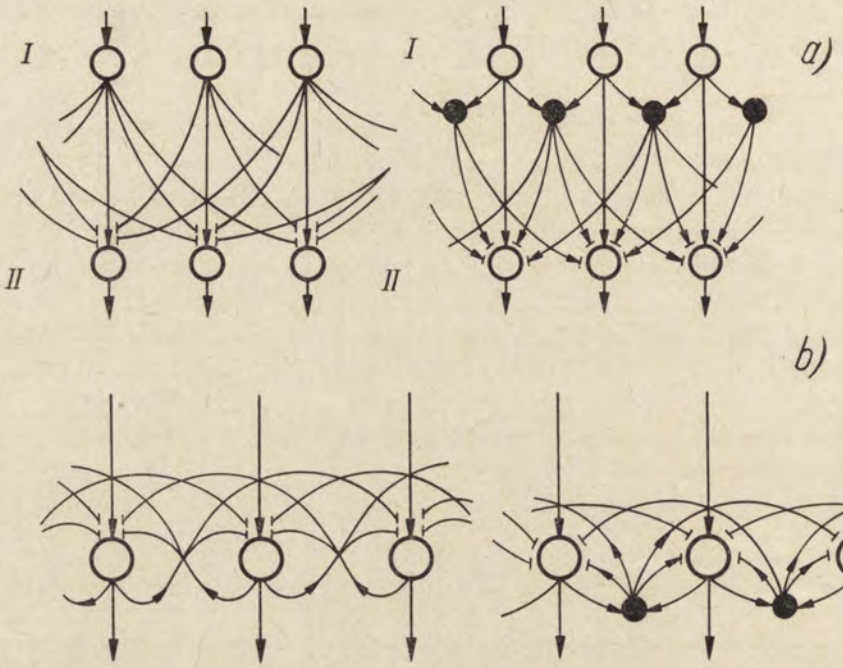

Fig. 15. One-dimensional structures (neuron chains) for two-layer (a), and one-layer (b) nets. Blackened circles denote inhibiting internuncial neurons

In consequence the question frequently raised as to the equivalence of one layer and two layer nets should be answered in the negative. This is even more obvious in view of the fact that in these nets non-linear elements such as neurons are involved. But even if we consider a case where every elements of the net operates in a linear range (i.e. in a range for which the rule of superposition holds), the two types of nets will differ in a certain aspect of their behavior. In fact the parameters of an element are never constant, and may change with time. It is possible to show (compare the example given below) that the effect of the changes of the parameters of the net elements will be markedly different for a net without feedback and for a net in which such feedback occur. This is closely related with the sensitivity of a net to local damage, but this problem requires separate consideration (Zmysłowski 1967).

Difficulties are also involved in finding such a mathematical description of the net with feedback, which would allow solution possibly in

a simple way of the basic problem consisting in our case in determining the output excitations for a given distribution of input stimulations and for the known structure and properties of an element. In one of the methods of introducing simplifications, use is made of structural symmetry, owing to which the corresponding formulae also show symmetry which, of course, makes the analysis easier. In our case this means that we have to do with symmetric matrices.

The general form of formula (1) describing the relation between the outputs and inputs in a two-layer net undergoes substantial changes when applied to one-layer nets since the values of the outputs (matrix $[Y]$) which should be determined will be included both in the right-hand and left-hand side of the formula. This results from that the output signal y is applied simultaneously to the inputs of other neurons. Hence we have a very complicated system of equations whose practical solution consisting of inversion of the matrices is difficult, and the results are incomprehensible. However, this difficulty may be reduced by introducing a certain change in the description and by making use of the symmetry of the structure.

Let us consider a simplified situation when the processes in the net do not go beyond the linear part of the characteristics, and the net is numbered in such a way that the particular elements may be counted by rows (as in a television display). The relation between the output and input is then described by the formulae:

— for a two-layer net

$$[Y] = [V]_{II}[W] \tag{5}$$

— for a one-layer net (with feedbacks)

$$[W] = [V]_{I}[Y] \tag{6}$$

It is interesting to note that the matrices $[V]_I$ and $[V]_{II}$ owing to the symmetry already mentioned may be represented using submatrices $[V]_s$ (formula 4), and the whole matrix has the same structure as the submatrices:

$$[V]_{II} = \begin{bmatrix} [V]_0 & [V]_1 & [V]_2 & \dots & [V]_h & 0 & \dots & 0 \\ [V]_1 & [V]_0 & [V]_1 & & & & & \cdot \\ [V]_2 & [V]_1 & [V]_0 & & & & & \cdot \\ \cdot & & \cdot & & \cdot & & & \cdot \\ \cdot & & & \cdot & & \cdot & & \cdot \\ \cdot & & & & \cdot & & \cdot & \cdot \\ \cdot & & & & & \cdot & [V] & 1 \\ 0 & \dots & 0 & [V]_h & & [V]_1 & [V] & 0 \end{bmatrix} \tag{7}$$

It was found that it is easier to invert matrices of this type, and hence it is possible to solve our problem, i.e. to compare the one- and two-layer nets (in the range considered). For this purpose Eq. (6) should be solved with respect to [Y]:

$$[Y] = [V]_{\mathrm{I}}^{-1}[X] \tag{8}$$

and compare the submatrices $[V]_{\mathrm{I}}^{-1}$ and $[V]_{\mathrm{II}}$ occurring in the matrices.

The conclusion of Reichardt and MacGintie (1962) may be applied to Eq. (8) since they refer to the stability of the solutions of equations of this type. It was found (Gawroński 1968) that the condition that the sum of lateral interactions (weights of lateral connections) for every element is smaller than unity is sufficient for the stability of the one-layer net described by the structural matrix $[V]_{\mathrm{I}}$ and only then the one- and two-layer nets may be compared. Otherwise the even smallest variations of the excitation produce in the closed loops of the one-layer net avalanche processes resulting in that the particular elements of the net are either brought to a state of saturation or blocked. An example of the excitation distribution for this situation is presented in Fig. 16.

A number of important properties of one-layer nets is explained by the example given below.

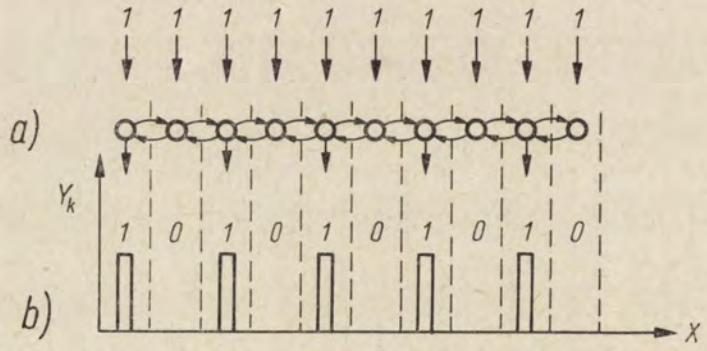

Fig. 16. Distribution of excitations in an instable one-layer net. A chain of neurons (a) is uniformly excited. As a result of mutual influences (when the values of weights are greater then 0.5) every second neuron is excited. The distribution of excitation for such an instable net is shown on (b)

4. AN EXAMPLE OF COMPARING ONE- AND TWO-LAYER NETS

Let us consider a net consisting of four elements as a simple but instructive example showing the possibilities of a structure with local feedbacks. We will introduce two kinds of connections between the ele-

ments (Fig. 17). To avoid unnecessary indices, we shall denote the weight of the connection between the nearest elements (V_{01}) by a, and that of connections between elements on the diagonal (V_{11}), by b. Furthermore,

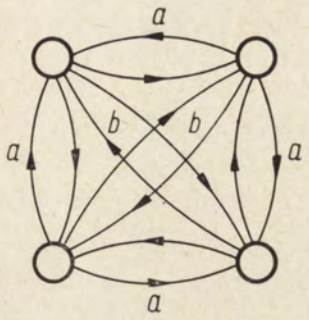

Fig. 17. Example of connections in a one-layer net

let us assume $V_{00} = 1$. Hence our structure is described by the matrix of connections:

$$[V]_{\mathrm{I}} = \begin{bmatrix} 1 & a & a & b \\ a & 1 & b & a \\ a & b & 1 & a \\ b & a & a & 1 \end{bmatrix}$$

To find a two-layer net equivalent to this structure for which we can give an easy interpretation of e.g. the character of the receptive field, it is necessary to find a matrix inverted to the former one. Of course the equivalence is understood here in the sense given above, i.e. in the range of linear operation of all elements and of stable operation of the system for constant values of the connection weights (here a and b), which means that the sensitivity of the processes in the net to weight variations is not taken into account.

The inverse matrix has the form:

$$[V]_{\mathrm{II}} = \begin{bmatrix} 1 & a & a & b \\ a & 1 & b & a \\ a & b & 1 & a \\ b & a & a & 1 \end{bmatrix}^{-1} =$$

$$= \frac{1}{[(1+b)^2-4a^2](1-b)} \begin{bmatrix} 1-2a^2+b & -a(1-b) & -a(1-b) & 2a^2-b^2-b \\ -a(1-b) & 1-2a^2+b & 2a^2-b^2-b & -a(1-b) \\ -a(1-b) & 2a^2-b^2-b & 1-2a^2+b & -a(1-b) \\ 2a^2-b^2-b & -a(1-b) & -a(1-b) & 1-2a^2+b \end{bmatrix}$$

The net considered in this example will be stable if the following conditions are fulfilled:

$$a < 1 \qquad b < 1 \qquad 1+b < 2a$$

As may be seen from the above formula, the excitability of this type of net, as distinguished from a two-layer net, is the greater the more e.g. the value b approaches unity (when the value of the denominator in the fraction preceding the matrix tends to zero). To render the physiological interpretation of the above example easier, the distributions of excitation and inhibition which would occur in the fields of the receptive elements of an equivalent two-layer net are shown in Fig. 18.

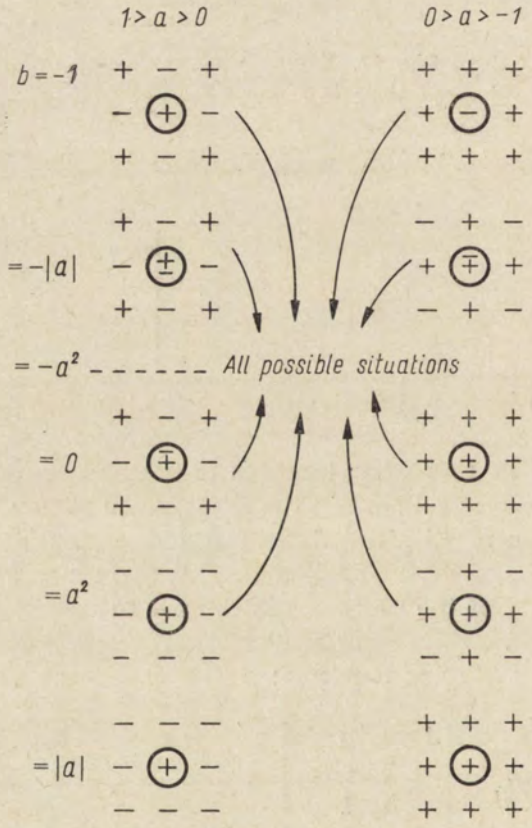

Fig. 18. Receptive fields which may generate in a one-layer net at various weights of connections

In other words, here the effect of stimulation of various elements of the net, neighbouring the element whose excitation is measured in the given experiment, is given. The excitation distributions are given for

different values of connection weights a and b. As may be seen from Fig. 18, a lateral inhibition (an on-center receptive field), a lateral excitation (an off-center field), and other more complex cases in which reactions analogous to those observed in the experiments of (Hubel 1964, Hubel and Wiesel 1965) are involved (hypercomplex cells), may take place. Receptive fields of the crossing type form, therefore, which are particularly suitable for detecting excitations of the shape of crossing and straight angles. It is easy to observe that like in the experiments of (Hubel 1964, Hubel and Wiesel 1965) a maximum response is obtained for the orientations of the stimulation excitation patterns rotated with respect to one another by an angle of 90°. Particularly interesting is the case when $b \approx a^2$. Small variations of the values of weights produce then a complete change of the receptive field involved, i.e. both of the on-center and off-center as well as of crossing type.

5. FINAL REMARKS

From the considerations given above and from the example presented it may be seen that in distinction from the two-layer net, it is not necessary to assume for the case of one-layer nets that cells with lateral connections (excitatory or inhibitory) of different type appear alongside. It suffices to make a fairly evident assumption that the values of connection weights show a slight deviation from a certain critical value, and hence in conformity with biological experiments, we obtain in a given layer cells with very different receptive fields. If we furthermore consider that in real structures much more connections exist and that certain asymmetries may also occur, we may conclude that nets of this type constitute an elastic system in which we may observe a number of different receptive fields. The latter may have concentric (on-center and off-center) as well as asymmetric forms.

The properties of the relatively simple structures which we discussed above will become richer if we assume that the particular connection weights may undergo changes under the influence of the signals or possibly stimulations of more diffuse character passing through them. Structures may then be proposed which will be capable of learning to react to stimuli of a given type.

It will be even more exciting to dispense with one more constraint, i.e. the delay in transferring signals between the particular cells. This will of course bring about the possibility of propagation of various kinds of waves and stimuli along the surface of the net, mutual interferences, and a number of other complicated phenomena which are always observed in biological experiments.

SUMMARY

The method of mathematical or physical modelling is found to be very useful in the explanation of some physiological phenomena, but the problem of adequate though simple description of the structure and elements inmediatable arises. In the report a method for describing of some neural nets is presented. Uniform nets of neuron-like elements which are arranged in two layer are described in the first part. Some properties of such nets enabling the detection of local features of simple images are shown. In the second part one-layer nets with local feedback loops are introduced and then they are compared with two layer nets without feedback. It was shown that with the help of one layer nets we can easily explain some results of neurophysiological experiments, for example the results of Hubel and Wiesel experiments on the visual tract.

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Acta Biol. Exp. 1969, 29: 335—358

Lecture delivered at the scientific session held in commemoration of the 50th anniversary of the Nencki Institute

December 1968

THE ROLE OF THE HYPOTHALAMUS AND AMYGDALA IN FOOD INTAKE, ALIMENTARY MOTIVATION AND EMOTIONAL REACTIONS

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Most of the authors working on the amygdala and hypothalamus would agree that these structures play an important role in the motivation and emotional behavior of the animals. Papez (1937) and then MacLean (1952, 1958) suggested that the limbic system together with the hypothalamus form the vital circuit concerned with the regulation of the most important functions of the organism such as food intake, defense against danger and procreation.

Beginning with Hess (1928, 1954) several authors evoked complex patterns of defensive behavior together with their emotional expression by stimulation of the hypothalamus and the amygdala on unanesthetized animals. These experiments were replicated in our laboratory on dogs and showed in addition that by stimulation of the hypothalamus it is possible to evoke three different patterns of aversive syndromes: fear and flight, fear and active defense, and rage with aggression (Fonberg 1963c, 1966a,b, 1967b). Fear-flight points may serve as a good negative reinforcement for the elaboration of avoidance reactions. Stimulation of the amygdala in its dorsomedial part also produces fear reactions in dogs, and it was also used as the negative reinforcement resulting in performance almost equal to the stimulation of "fear" points within the hypothalamus (Fonberg 1963b, 1966a, 1967b). It was also shown by many authors that the hypothalamus and amygdala mediate and motivate sexual functions. All

these findings lead to the suggestion that the physiological mechanisms of the amygdala and hypothalamus are parallel in respect to many functions.

In this paper I shall concentrate on alimentary functions and consider chiefly our recent experiments on dogs.

The role of the hypothalamus in alimentary mechanisms is very well known and has been studied in the last few decades by many investigators. In their classic work Anand and Brobeck (1951) divided the hypothalamic mechanisms into two opposite parts — a "feeding center" situated in the lateral hypothalamus, and a "satiation" center in the ventromedial hypothalamus. After these findings it was well established by multichannel studies of many investigators that lesions of the ventromedial hypothalamus result in overeating, and that large lesion in the lateral hypothalamus produce aphagia and adipsia. Stimulation of these areas yields reverse effects. The conclusions which these facts suggest is that the lateral hypothalamic area is the positive "center" for the regulation of food intake behavior, whereas the ventromedial hypothalamus in respect to food intake may be considered as an inhibitory center (Fig. 1).

Fig. 1. Schematic localisation of the "feeding center" in the lateral hypothalamus (L), and "satiation center" in the ventromedial hypothalamus (VM)

Later, experiments of Grastyan et al. (1956), Wyrwicka et al. (1959, 1960), Miller (1957), Coons et al. (1965) and others showed that not only the food intake, i.e. the unconditioned alimentary act, but that also the instrumental alimentary reaction are mediated by the lateral hypothalamus. Wyrwicka showed that stimulation of the lateral hypothalamus on satiated goats evoked not only the act of eating but also the performance of the instrumental reactions, which were trained before the stimulation. The author concluded therefore that the reflex arc passes through the lateral hypothalamus. These facts were the basis for Wyrwicka's theory concerning the mechanisms of alimentary instrumental reactions (1960,

1966a). A somewhat different hypothesis was formulated by Konorski (1967).

Wyrwicka also showed that during stimulation of the lateral hypothalamus on satiated goats it is possible to train and differentiate new instrumental reactions. Lateral hypothalamic stimulation transforms a previously satiated animal, indifferent to food, into one who starts to eat voraciously and performs all previously learned instrumental reactions necessary to provide food. This fact might mean that the stimulation evokes the state of hunger in spite of the stomach being full. These experiments as well as those described by other authors incline one to the conclusion that the lateral hypothalamus acts as the "hunger center".

Recent experiments of Hoebel and Teitelbaum (1962) on rats and my experiments on dogs (Fonberg 1967b) showed that the problem is more complicated. If the lateral hypothalamus is only the "hunger center" its stimulation should be "unpleasant" and dogs should learn to avoid it. The results of our experiments showed however the opposite effect. In fact, it was not possible in dogs to establish the instrumental reactions in order to avoid the stimulation of the lateral hypothalamic area, although stimulation of the same points on satiated dogs provoked eating. On the contrary, it was very easy to establish the instrumental reactions using stimulation of the same points as the reward.

The results of the experiment performed on three dogs displayed in Fig. 2 indicate clearly that it was possible to establish an instrumental reaction to an acoustic stimulus (Tone) reinforced only by brain stimulation of a "hunger" point without food being given (Fig. 2A). When the

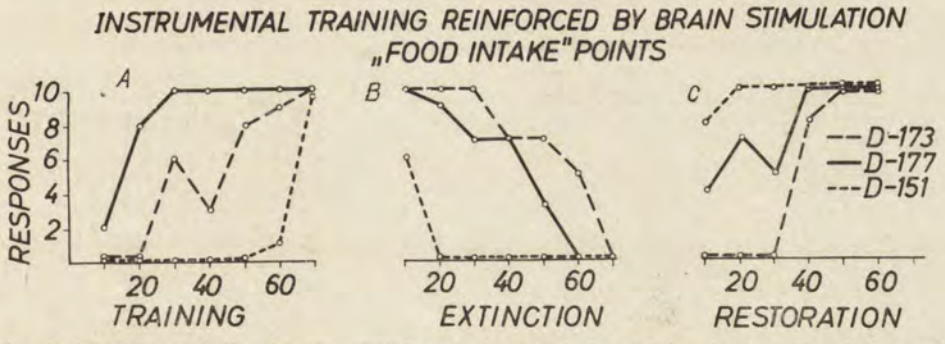

Fig. 2. Training of the instrumental reactions reinforced by brain stimulation of "feeding center", A, training, B, extinction, C, restoration

conditioned stimulus was no longer reinforced by brain stimulation the instrumental reaction became extinguished (Fig. 2B). However, it was easily restored when the conditioned stimulus was again followed by brain stimulation (Fig. 2C). These facts seem to indicate that, for the

instrumental training, stimulation of the feeding system possesses properties of reward similar to food intake.

The same conclusion seems to follow from the next experiment, performed on two dogs. These animals were previously trained to perform to the conditioned stimulus (Tone) an instrumental reaction (bar pressing) reinforced by food. When in the crucial experiments, brain stimulation of an alimentary point was substituted for food reinforcement, full transfer occurred. When these two reinforcements were given alternately in blocks of five trials each, the dogs performed the instrumental reaction in 100% of trials, i.e. equal to the conditioned stimulus reinforced by food intake or brain stimulation (Fig. 3A). The dogs seemed not even to notice the shift.

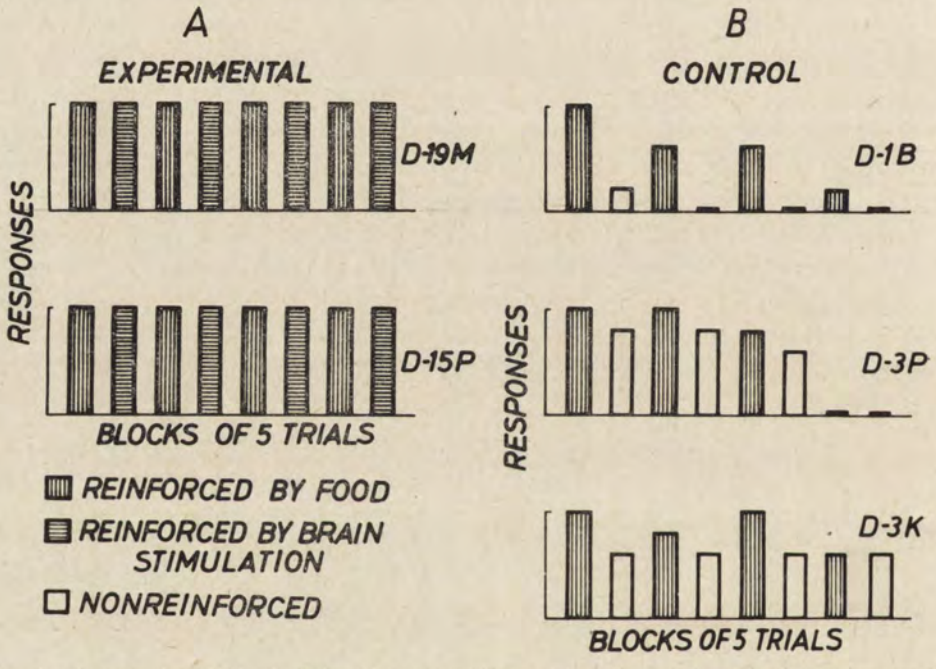

Fig. 3. Experimental: The instrumental reaction is reinforced either by food (perpendicular stripes), or by the stimulation of the "feeding center" (horizontal stripes). The performance of the dog in spite of the shifts in reinforcement in every five trials, keeps the maximal level of performance. Control: the instrumental reaction is either reinforced by food (perpendicular stripes) or nonreinforced (white). In these last conditions the instrumental reaction show a tendency to partial extinction

In the control animals where the schedule was the same i.e., five food reinforcements were given to the conditioned stimulus alternately with five trials non-reinforced (that is where brain stimulation was no longer

applied) partial extinction occurred (Fig. 3B). The differentiation of two conditioned stimuli, trained to food reinforcement, was also fully preserved when food was substituted by cerebral stimulation. These facts lead to the suggestion that stimulation of lateral hypothalamus has the properties of food reinforcement rather than hunger. Our results are consistent with those obtained by Margules and Olds (1962) and Hoebel and Teitelbaum (1962) by the method of selfrewarding. In their method however, because of the short trains of stimulation employed (1/2—1 sec after each press), the offset of stimulation almost immediately followed its onset. Therefore the adherents of the drive-reduction theory might claim that the offset of stimulation, i.e. — the decrease of hunger drive is rewarding. In our experiments the long time of on-stimulation (10—20 sec, and in special series of experiments even up to 60 sec or more) excludes this criticism.

All these facts reveal the existence of another aspect of the function of the hypothalamic food system, which cannot be accounted for by an increase of the hunger drive activity. If stimulation increases hunger, it is difficult to explain why it acts as a reward. Why would deprived animals perform a reaction which resulted in increasing their hunger and repeat it for hundreds of trials? One would rather expect the opposite i.e. that an increase of hunger should serve as punishment.

It seems that our results can be understood by assuming that stimulation of the hypothalamic food system does not produce augmentation of hunger but rather a state equivalent to food intake. This is in agreement with the formulation of Hoebel and Teitelbaum (1962). Developing further this idea we may hypothesize that hypothalamic stimulation produces various sensations similar to those caused by food intake i.e. smell and taste of food (Wyrwicka 1966a, Fonberg 1967b).

The sensory reward (i.e. pleasant smell, taste and perhaps some kind of central equivalent of prioproceptive and interoceptive feedback, which usually accompanies food consumption) is probably not the whole effect of lateral hypothalamic stimulation, which serves also as a kind of general energizing agent, and this energy is pleasant for the subject — we may call it "joy of life". One dog was observed who after extensive brain lesion with subsequent meningitis was in a very weak and energic state. He could not walk, spent most of the time lying down, apathetic, he hardly accepted food, and had to be carried to the experimental room, where he hung down on the harness, legs bent, head down. After stimulation of the lateral hypothalamus he not only ate voraciously, but he stood up on his legs, head high, and after the experiments he ran back to his cage, where for half an hour to one hour he was able to walk and showed an interest in the environment and humans. Stimulation of the

lateral hypothalamus not only enhanced his alimentary drive but provided him with a source of energy and joy for the activity of life.

Lesions of the lateral hypothalamus have opposite effect the, also taking out much more than the hunger drive.

Lesions of the lateral hypothalamus on dogs (Fig. 4) as shown by Fonberg and Rożkowska (1968) and Rożkowska and Fonberg (1970) produces aphagia, followed by hypophagia, vomiting and loss or impairment

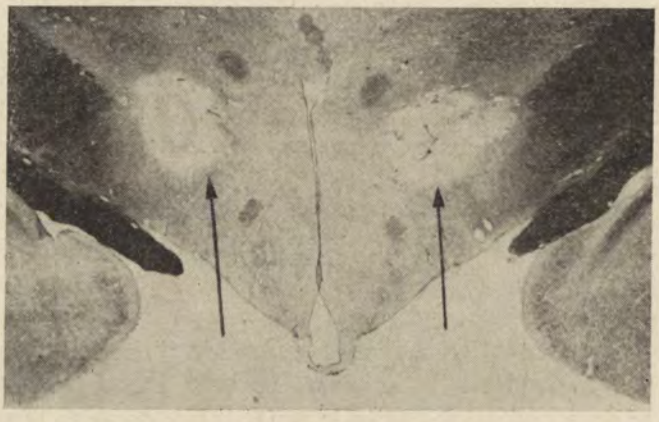

Fig. 4. Photograph of a typical lesion of lateral hypothalamus in dog

of instrumental reactions. Moreover, the dogs are hypotonic, spend most of the time lying down, they lose their interest in the environment, and do not approach food. They reveal negativism, catatonic-like symptoms and sometimes they adopt bizarre positions or habits. All these symptoms are described in more detail in a separate paper (Rożkowska and Fonberg 1970). Similar observations were made by many authors on rats, cats and rabbits (Wyrwicka 1957, 1966a, Morgane 1961b, Teitelbaum and Epstein 1962, Teitelbaum 1964, Balińska 1963 and others). We choose the dog as subject for our experiments because all the emotional and motivational changes are much more pronounced and striking in dogs than in rats or cats, because of their close social relations with humans and lively emotional expression.

Before discussing the symptoms obtained by hypothalamic lesions I shall describe the very similar effects of the amygdalar lesions which have been also performed on dogs. The amygdaloid complex is much less investigated concerning the alimentary mechanisms than the hypothalamus. Most of the investigators studied the role of the amygdala in defensive reactions (for references see Fernandez de Molina and Huns-

perger 1962). The decrease or enhancement of alimentary functions was mentioned by some authors mostly as a byproduct of other experiments, and were not the subject under special study.

The amygdaloid complex is composed of several nuclei which may be divided into two parts (basolateral and dorsomedial) (Fig. 5). Stimu-

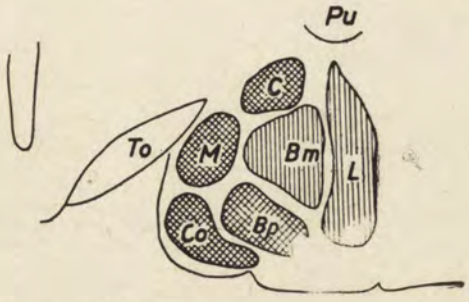

Fig. 5. Schematic representation of the nuclei of the amygdaloid complex. The nuclei of the baso-lateral and dorsomedial parts are distinguished by different stripes

lation of the dorsomedial part on dogs, besides evoking defensive reactions (Fonberg 1963c, 1967b), may also produce alimentary responses such as salivation, chewing, retching, and an increase of food intake as recently shown by Robinson and Mishkin (1962), Grossman and Grossman (1963), Koikegami (1964), and Lewińska (1968), on other species.

Lesions of the dorsomedial part on dogs produced aphagia (Fonberg 1966c, 1968, 1969, Fonberg and Sychowa 1968) which lasted from a few days to two weeks, and was followed by a longlasting period of hypophagia. The dogs were also adipsic, showed food preference and vomited. Besides, similarly to the hypothalamic lesions the dogs were apathetic, spent most of the time lying down, they are not interested in the environment, looked sad and driveless, did not greet their experimenter, did not jump, play or strive for food. They seemed to be placid and quiet, but at the same time some of them were more irritable and aggressive toward other dogs. Sometimes they showed bizarre postures, like standing on two legs and leaning against the wall, placing their head on the bar etc. They also showed some signs of negativism. The normal dog goes willingly to the experimental room where he is fed, jumps up to the stand and readily lifts his legs to enable him to be put in the harness. The amygdalar dogs withdraw from their leaders, resist going to the experimental room, do not want to jump on the stand, and oppose all manipulations.

Similarly to the hypothalamic dogs, in the first period of aphagia, they not only are not interested in taking food themself but they fight against being fed by force, split out the food, try to escape vigorously, reject the bowl with food and even may bite the experimenter to avoid forced feeding. Later, they accept passive feeding and they swallow the food if it is inserted deeply into the mouth. Then they start to eat themselves, but still they have to be baited by many means would not approach the food bowl but had to be served to "their nose". Sometimes they started to eat only after they tasted food placed on their tongue. All the dogs showed food preference, therefore they have to be fed only with a special kind of food. It is interesting to note that most of the amygdalar and hypothalamic dogs preferred sweet food like eggs with sugar, than meat, which is the preferred meal of normal dogs. On Fig. 6 the average daily food intake is shown in the five days before the operation, after the operation and six weeks subsequently.

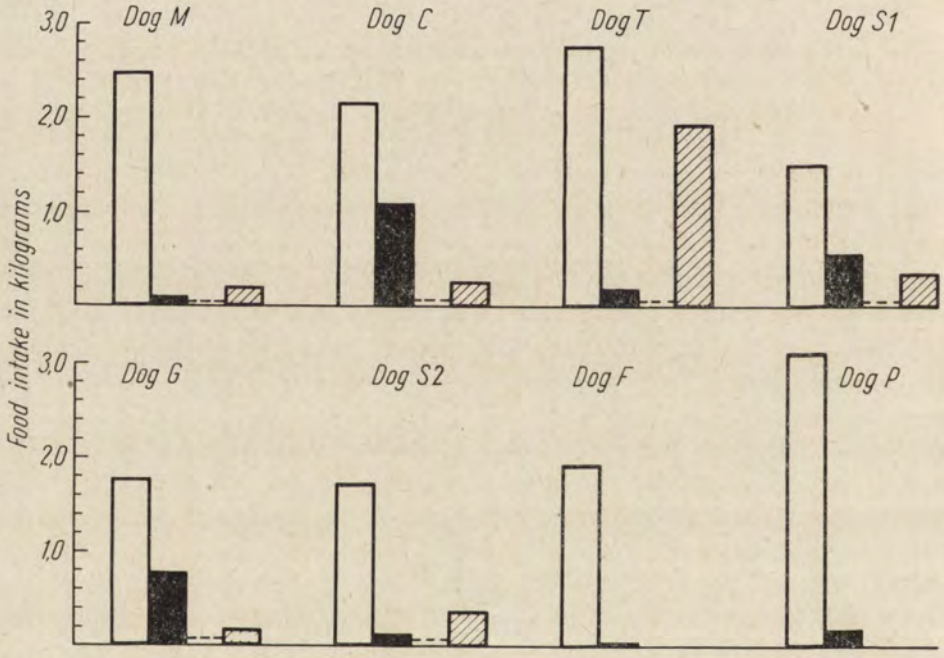

Fig. 6. Bars represent daily food intake (mean from five days), for each dog, before the operation, just after and two months later

It seems worth noting that one very consistent symptom, which was observed both after lateral hypothalamic and medial amygdalar lessions, and which was not described previously by other authors, was vomiting, which outlasted aphagia for a few weeks (Fonberg 1968). The dogs vo-

mited not only during the period of aphagia when they were force-fed but also in the subsequent period of hypophagia and even in some cases after the recovery of the alimentary functions. Vomiting appeared from a few minutes up to half or even one hour after feeding. This last symptom may possibly be caused by changes in the functions of the stomach. As recently shown by Glavcheva, Rożkowska and Fonberg (in press) after lateral hypothalamic lesions the stomach contractions are greatly changed.

The instrumental reactions established before the operation were deeply impaired, and even after long retraining, in the period of the recovery from aphagia when dog ate voluntarily, the instrumental performance was not perfect. During the period of aphagia instrumental reactions were completely abolished. Afterwards, though the dogs ate voluntarily, they did not show interest in the food-bowls, they did not react to the noise of turning the food-tray and they did not perform the instrumental reaction. In most of the dogs retraining by means of passive movements or other procedures was possible although it lasted longer than primary training and even then instrumental reactions were irregular and fluctuating and from time to time the periods of complete arreflexia occurred (Fig. 7).

The postoperative training of the instrumental reactions was also greatly impaired in comparison with the normal training. In two dogs the instrumental reactions was not retrained after several months (1360 and 1500 trials), (Fig. 8). It is worth noting that most of the authors like Wyrwicka, Balińska, Teitelbaum and others observed the recovery of the instrumental reactions after lateral hypothalamic lesions on rats and cats. Wyrwicka (1966b) described that after rostral hypothalamic lesions the instrumental reactions were present in spite of the aphagia. In our cases the total aphagia was always transient. It lasted from one or two days to three weeks and the food intake always recovered earlier than the instrumental reactions. In six dogs after hypothalamic lesions and in two dogs after amygdala lesions the instrumental reactions were not restored after several months of training. In these last cases however the fibres of the internal capsule were damaged at least unilaterally (see Fig. 9). So it might be suggested that the fibers from the internal capsule to the lateral hypothalamus — i.e. connecting the motor system with the alimentary system, are important for the instrumental mechanisms. The other possibility is that the connections from the extrapyramidal system i.e. pallido-hypothalamic fibres might be damaged and that they are the most important in this respect (see also Morgane 1961a).

At the present time, from the results of our work we may conclude

that, at least by methods used in our experiments, we were not able to find the obvious differences between the functions of the lateral hypothalamus and dorsomedial amygdalar region in respect to food intake

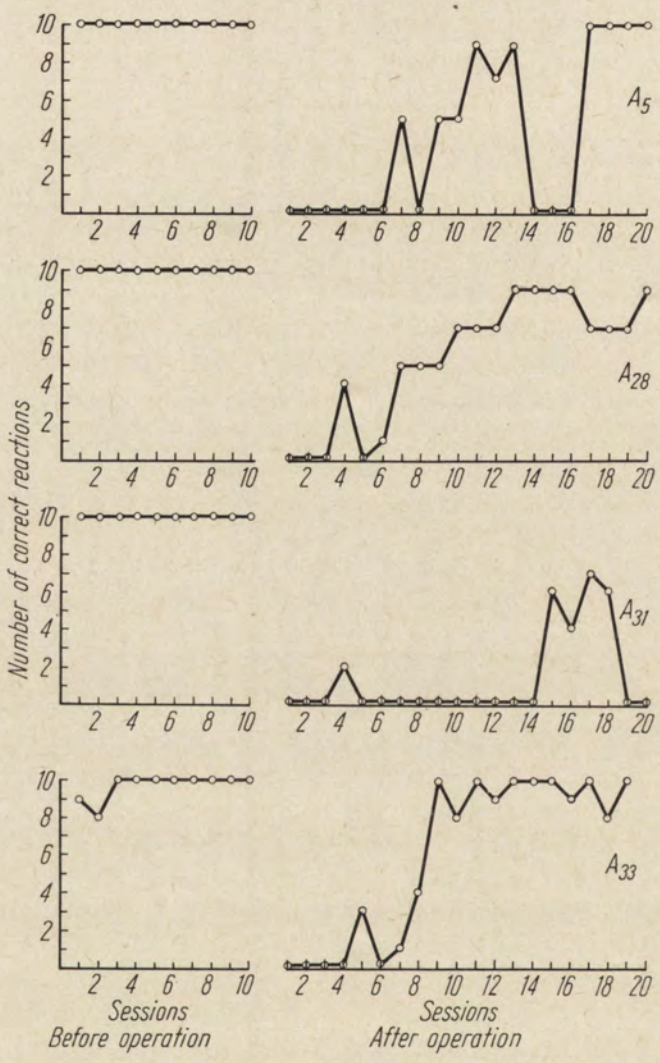

Fig. 7. Postoperative retention of the instrumental alimentary reaction for each dog

and instrumental alimentary reactions. It seems to indicate that alimentary functions are doubled in these two structures.

The only objection which might be suggested was, whether it really is the amygdala itself, which is important in alimentary mechanisms and not the neighbouring structures, like the entopeduncular nucleus, globus

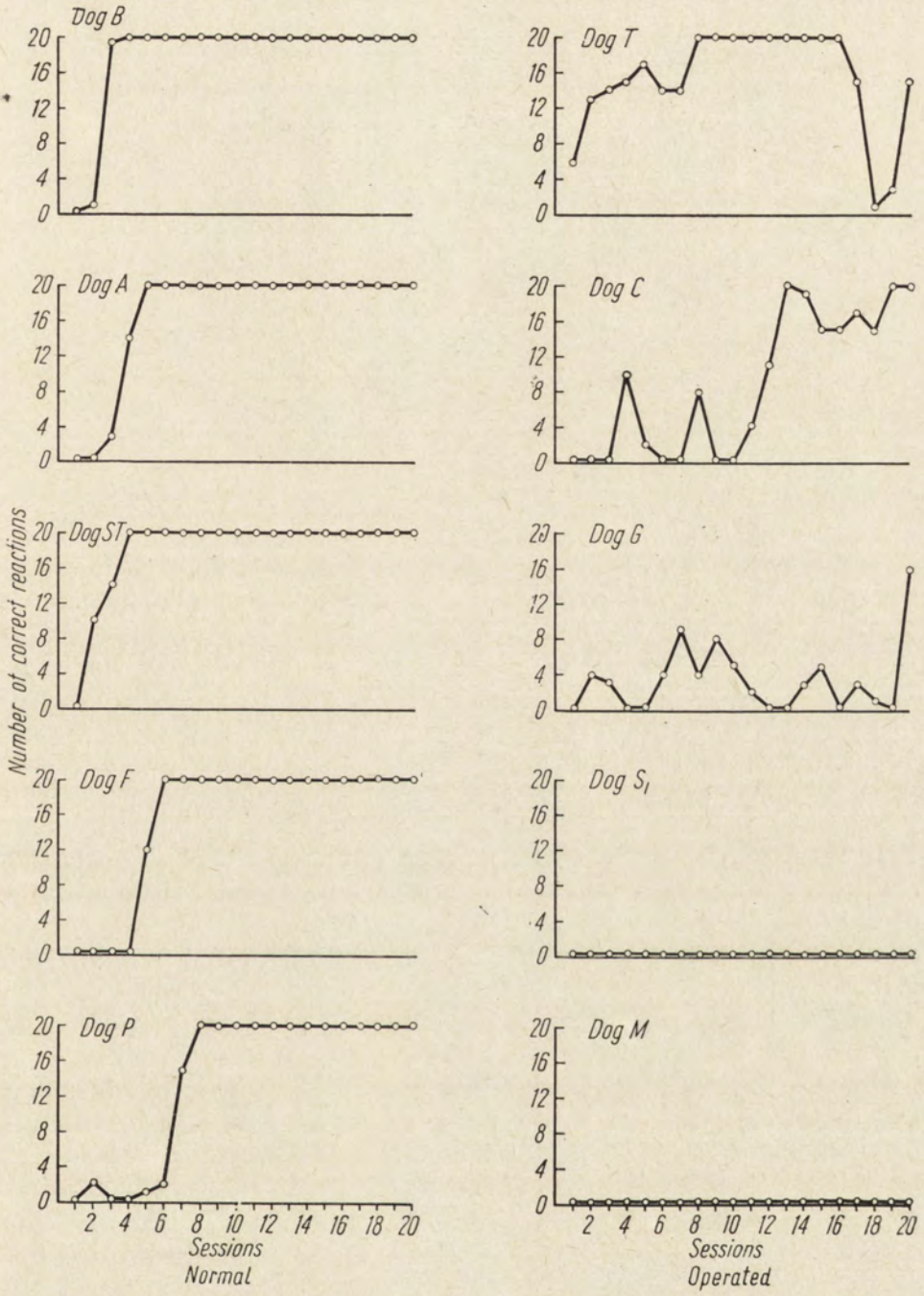

Fig. 8. Training of the instrumental alimentary reaction after dorsomedial amygdala lesions (operated), as compared with control (normal). Training of each dog is shown separately

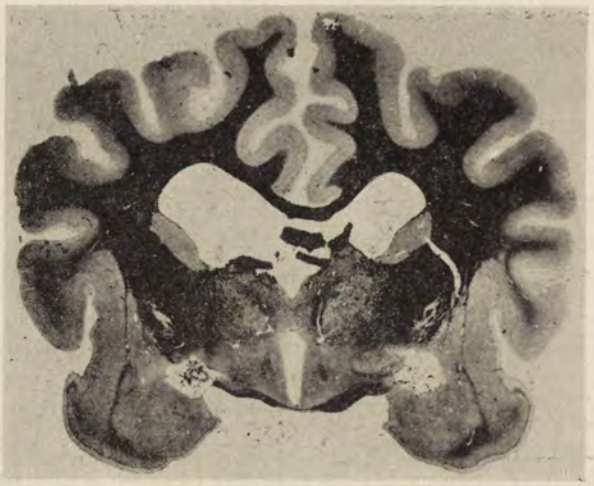

Fig. 9. Photograph of the typical amygdalar lesion, of the dog in which instrumental alimentary reactions are irreversibly impaired after operation

pallidus, or pallidofugal fibers. Therefore, it seemed very important to find which structure is, in fact, "responsible" for the amygdalar aphagia.

As was mentioned, the hypothalamus was much more investigated in respect to alimentary functions than the amygdala. Although, some authors notice aphagia in cats and rats after amygdalar lesions (Anand et al. 1958, Wood 1958, Yamada and Greer 1960, Anand 1961, Ward 1961, Kling and Schwartz 1961, Koikegami 1964, Ursin 1965), the strict localization of this phenomenon was not studied. The first case of longlasting aphagia on a dog after amygdala lesion was reported by Brutkowski et al. (1962). In this experiment the lesions, made by suction, involved the whole amygdala and exceeded the amygdaloid complex, damaging the globus pallidus, the entopeduncular nucleus and the internal capsule. Therefore, it was suggested that the damage of these structures and not the amygdala may be important in aphagia.

In the next series of experiments performed on ten dogs (Fonberg and Sychowa 1968), the lesions were made stereotaxically by electrocoagulation, but they were still rather large as they involved several amygdaloid nuclei, and extended dorsally beyond the amygdaloid complex. However, as in all aphagic dogs the central and medial amygdalar nuclei were damaged at least unilaterally, so it was suggested that the damage of these very nuclei might be responsible for the amygdalar aphagia.

The most recent series of experiments were concerned with detailed studies on the localization of the amygdalar "food center" (Fig. 10).

Using the method of small electrolytic lesions it was possible to detect a restricted area within the amygdaloid complex, the lesion of which produces the whole, syndrome of amygdalar aphagia described above. As is shown on Fig. 11 aphagia may result from the damage of a small

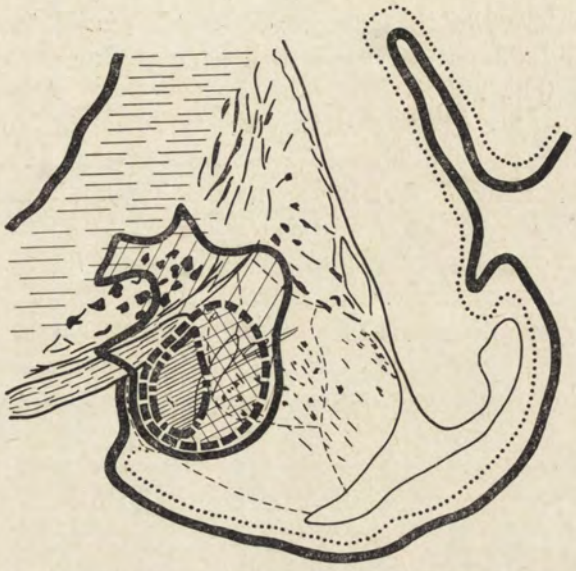

Fig. 10. Scheme of the dimensions of typical amygdalar lesions, during gradual steps to approach to the area "critical" for aphagia

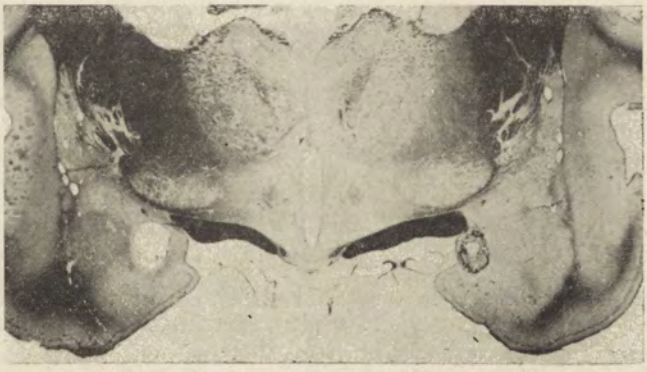

Fig. 11. Brain section photograph showing small lesion situated in medial amygdala, which produced aphagia with subsequent longlasting hypophagia

amygdalar area, localised in the region of the central and medial nuclei not exceeding the amygdaloid complex and not invading other amygdalar nuclei. In these very dogs the instrumental performance was unfortuna-

tely not tested. In these particular cases the total aphagia was transient, lasting only one to five days, but nevertheless the subsequent hypophagia was very persistent and for several months it was so pronounced that, for example, the dogs which usually consumed an average of two kgms, after operation never ate more than 200—300 gms. It also happened that on certain days of this late postoperative period they refused completely to take food. On the basis of these experiments we feel justified in concluding that aphagia may be produced by a lesion within the amygdaloid complex itself, and that the dorsomedial amygdalar region is crucial in this respect. Therefore we may speak about un amygdalar "food center" similar to that in the lateral hypothalamus.

The confluence of the symptoms observed after the lesions of lateral hypothalamus and dorsomedial amygdala (the hypothalamic and amygdalar syndroms) is striking. In both cases aphagia, adipsia and vomiting and, after the recovery from complete aphagia, longlasting hypophagia and food preference occurred, and in both cases apathy, loss of motivation in the alimentary responses and an almost complete loss of interest in the environment and lack of friendly relations with humans were noted. Similarly, both after hypothalamic and amygdalar lesions severe impairment of the instrumental alimentary reactions was observed, concerning retention of the response trained before the operation and postoperative training. In both cases, in spite of the indifference and apathy, we sometimes notice increased irritability and agressiveness. Therefore without further investigations it is not possible to say that some particular alimentary functions are more impaired by hypothalamic lesions, than by amygdalar destruction, or vice versa, for example that in one case motivation, in the other the food intake ability, or instrumental performance are differentially affected. On the contrary, lesions in each of these areas impair in a similar way most of the alimentary functions, motivational and consummatory, together with their emotional aspects.

As was demonstrated, we observed in both cases loss of motivation, and this was not only loss of the specific alimentary drive, loss of hunger, but at the same time a lack of some kind of general drive, absence of energy, loss of the "joy of life". The dogs were sad, indifferent, did not jump, did not play, did not greet their experimenters. This general look of deep sadness was very striking and reminiscent of patients during the depressive state or schizophrenia. Nothing is worth an effort. The animals not only do not seek and do not struggle for food, but if food is presented they are not interested in approaching it, and if they start to eat they eat slowly and fastidiously, spitting the food out, pushing away the bowl etc. (Fig. 12). Speaking psychologically the dog after operation not only does not seem to be hungry, but he does not like to eat, he does not enjoy

food, he is not anxious to consume it and he is not motivated to do anything to get the food. As already said, but here stressed again, both hypothalamic and amygdalar lesions produce a very similar effect.

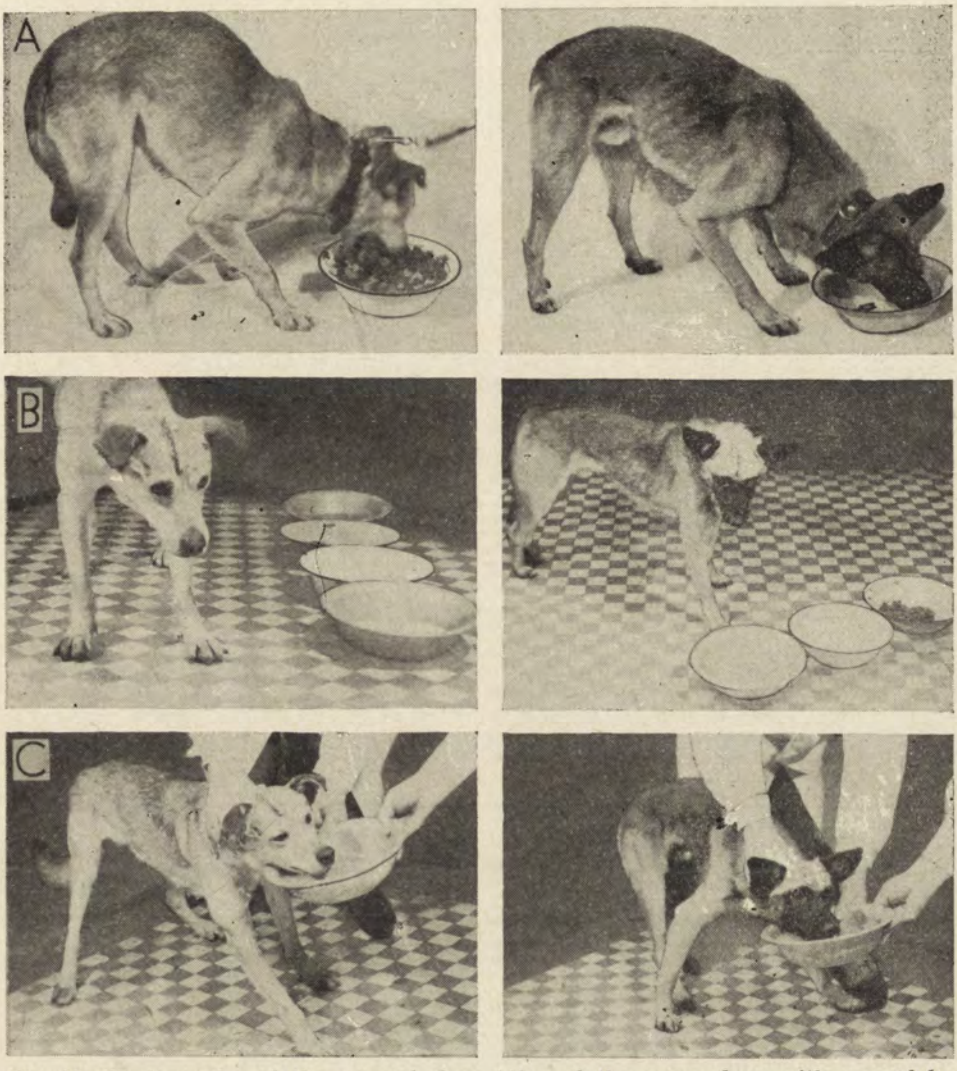

Fig. 12. Photographs of the normal dogs (A) and the same dogs with amygdalar aphagia (B) and (C). Notice the sad look of the animals their indifference to the food "cafeteria", and their resistance to feeding

What are therefore the functional relations between the amygdala and hypothalamus?

Several authors including myself (Fonberg 1967a) considered the amygdala as the "center" of the "upper rank" put upon the more

"effector" centers, like the hypothalamus. The amygdala being the phylogenetically older forebrain structure was considered as possessing a general regulatory role, differentiating qualitatively the complex stimuli from the surrounding and integrating and regulating the most important biological functions.

From our present experiments it follows that the functions of dorsomedial amygdala and lateral hypothalamus are in many respect similar and that one can talk about the "double" representation of the alimentary functions. As shown by Nauta (1962) and Valverde (1965) the anatomical connections of these structures are very well developped. This support the suggestion of their belonging to the common system.

On the other hand the motivational alimentary system seems to be not limited to the hypothalamus and amygdala. We should not think in terms of strict localization of certain, particular functions like hunger, reward, and instrumental mechanisms, but speak rather about the excitatory — inhibitory balance of the whole alimentary system, which, as we know, extends beyond the hypothalamus and amygdala.

Our recent experiments seem to indicate that probably most of the symptoms of hypothalamic and amygdalar aphagia and atony are caused by the inhibitory influences from the inhibitory centers which prevail on the excitatory ones and supress the remaining structures of the alimentary system. One source of this inhibitory influence is probably the ventromedial hypothalamus. The inhibitory role of the ventromedial hypothalamus upon the alimentary mechanisms is very well known from the numerous experiments of many authors on cats and rabbits. And recently Rożkowska found the same effect on dogs (personal communication).

The second source of the inhibitory influences upon the positive alimentary functions may derive from the lateral amygdala. From our experiments with Delgado, on cats (Fonberg and Delgado 1960, 1961ab), and also from the experiments on dogs (Fonberg 1962, 1963a, 1967a) it follows that stimulation of the lateral amygdala produces inhibition of food intake in hungry animals, and also the inhibition of the alimentary instrumental reactions.

On the other hand, our recent experiments showed (Fonberg, in preparation) that, the damage of the lateral amygdala (Fig. 13) produces hyperphagia on dogs (Fig. 14). These last results are consistent with the results obtained by Green et al. (1957) and Morgane and Kosman (1957, 1959) on cats. In dogs however, hyperphagia is not so evident because normal dogs are hyperphagic, i.e. if food is presented they quickly run toward it, they consume it voraciously, and take much more food than they really need (if they are not spoiled as pets).

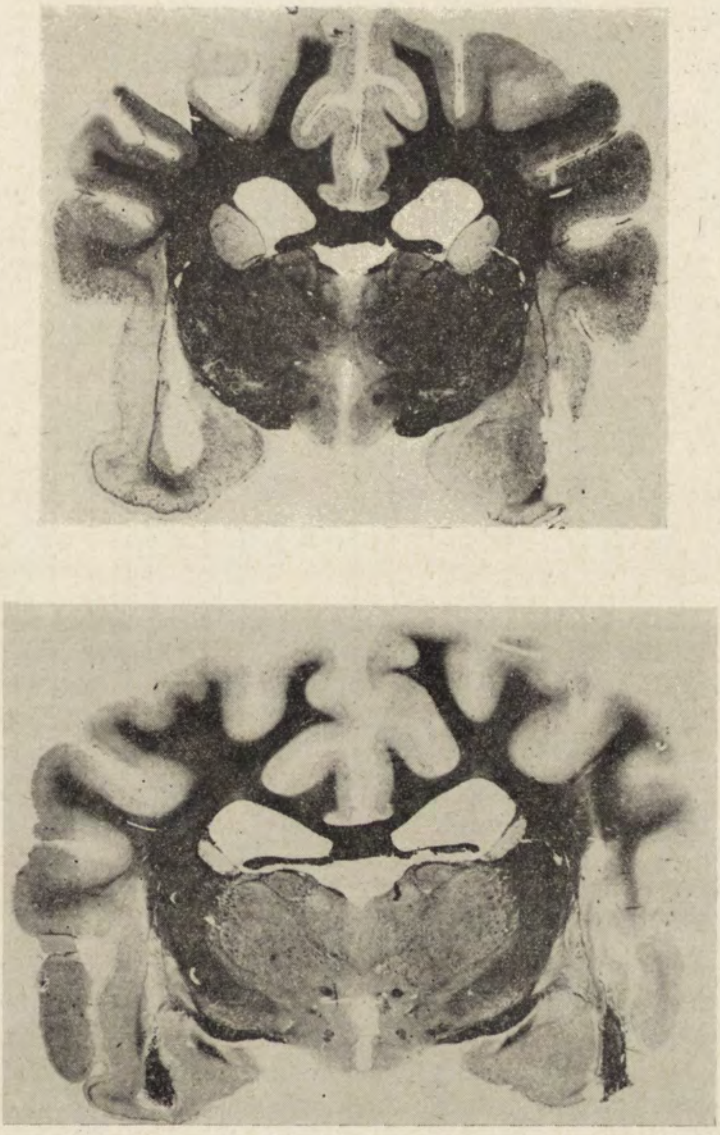

Fig. 13. Typical photographs of lesions in lateral amygdala, which produced hyperphagia in dogs

Dogs with lateral amygdalar lesions are very mild, docile, friendly, lively and playful like puppies, and like puppies they are interested in their surroundings. Their instrumental alimentary performance was usually not changed, and it was not so easy to notice the difference between these dogs and the normal ones.

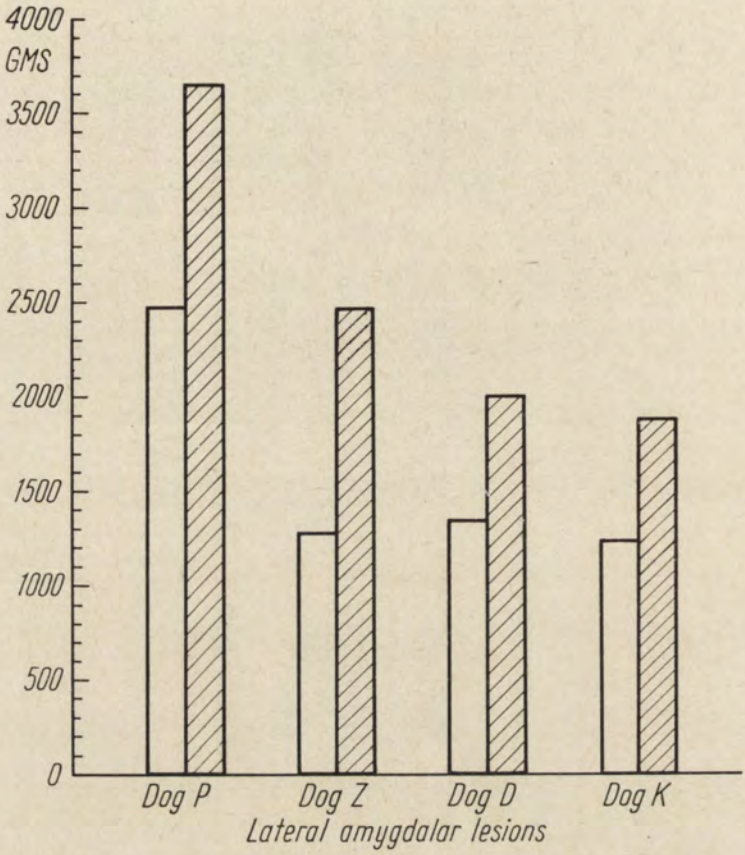

Fig. 14. Bars represent daily food intake (mean from five days) for each dog before operation (white bars) and after lateral amygdalar lesions (striped bars)

The effect of lateral amygdalar lesions however is striking if these lesions are performed on the hypophagic dogs, previously damaged either in the lateral hypothalamus (Fig. 15) or in the medial amygdala. In such cases the previously hypophagic and atonic dogs started to eat voraciously from the first day after operation and what is more, their general behavior become again lively and friendly. All the "psychic" signs of atony, apathy and depression disappeared suddenly after lateral amygdala lesions (Fig. 16).

What does it mean? The damage of the "alimentary centers" either hypothalamic or amygdalar was still present. Now, the animals had in addition further damage so, why then should they became more "normal" thereafter? How can the animal be "better" with two lesions in the brain, than with a single one?

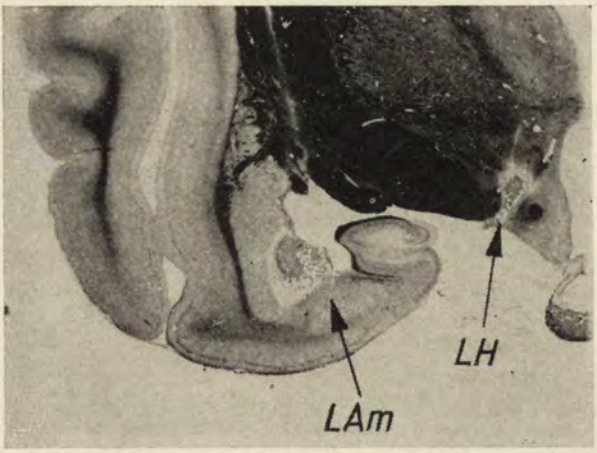

Fig. 15. Brain section photograph of the dog with lesion in lateral hypothalamus, which produced aphagia, with subsequent hypophagia, and with second lesion in lateral amygdala resulting in prominent hyperphagia and restoration of vital energy

These facts seem to show that the lateral hypothalamus and medial amygdala, cannot be thought of as unique "alimentary centers" damage of which will abolish irreversibly all the alimentary dispositions. It is probable that a lesion of the lateral hypothalamus or the dorsomedial amygdala takes out the source of energy which may be called specific alimentary motivation and morever some kind of unspecific energy leaving the organism under the prevailing influence of the inhibitory centers which results in depressive symptoms.

A similar conclusion may follow from the experiments of Skultety (1968) who observed aphagia after lateral hypothalamic lesions, which was effaced by subsequent lesion within the mesencephalon. Similarly, as in our cases of lateral amygdalar lesions, in spite of the existing damage of the hypothalamic "feeding center", the animals became to eat normally as a consequence of a subsequent mesencephalic operation. The whole problem seems to become then the problem of homeostasis, the balance of the inhibitory and excitatory influences being the most important.

We should mention now that particularly after the posterior hypothalamic lesion all the symptoms are more severe and longlasting than after amygdalar and anterior hypothalamic lesions. Deeper changes after the posterior hypothalamic lesions may be related to disrupted connections with the reticular formation, because of the strong source of energy which is cut in these cases. It may show that it is not the disruption of the reaction pattern but rather the lack of energy which would be then the cause of pronounced depressive symptoms in the lateral-posterior

hypothalamic dogs. In particular the general apathy and changes in emotional reactions are the most pronounced in the posterior hypothalamic syndrome and they are very similar, at least in their superficial appearance, to the human's psychoses and neuroses, like depressive states, or even schizophrenia. Negativisms, catatonic symptoms and bizarre positions, apathy, loss of energy and, at the same time, irritability are more often observed after large hypothalamic lesions, although on most of the amygdala dogs all these symptoms were also present (see Fig. 12 and 16).

Fig. 16. Photographs of the dog with dorsomedial amygdalar lesion, which produced aphagia and fearfulness (A), and the same dog after subsequent lateral amygdalar lesion (B) and (C). Notice the withdrawn posture of the dog with dorsomedial lesion and his resistance to pulling by the leash (A), and the normal, lively posture of the same dog after subsequent lateral amygdalar lesion, his friendly attitude toward the human hand (B) and willing food intake (C)

It is interesting to note that in humans tumors of the third ventricle, involving hypothalamus or tumors of the temporal lobe involving amygdala, were very often diagnosed as schizophrenia, because of the resemblance of the symptoms in both cases (Malamud 1967).

So, although it would be to go too far into speculations, to hypothesize that functional changes within the hypothalamus and limbic system may be the cause of depressive neuroses or psychoses like schizo-

phrenia, in the analysis of the mechanisms of these illness, the observations on dogs described above may be helpful and should be taken into consideration.

SUMMARY

The physiological role of the hypothalamus and amygdala with special reference to alimentary function was discussed. The results of our experiments on dogs were analysed and summarized as follows. (i) Stimulation of the lateral hypothalamus evokes food intake and serves as positive reinforcement for instrumental reactions, whereas lesions of the same area produced aphagia, vomiting, apathy, impairment of the instrumental reactions, negativism and loss of vital energy. (ii) A similar effect is obtained by dorsomedial amygdala lesions. (iii) Lesions of the lateral amygdala produce hyperphagia and an increase of body weight which resemble the effect of ventromedial hypothalamic lesions.

It was suggested that most of the alimentary functions have double representation, in the hypothalamus and in the amygdala.

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Lecture delivered at the scientific session held in commemoration of the 50th anniversary of the Nencki Institute

December 1968

VISUAL FIXATION REFLEX: BEHAVIORAL PROPERTIES AND NEURAL MECHANISM

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I. INTRODUCTORY REMARKS

From a theoretical point of view, the retina might be so built that an object would be sharply seen independently of its image location. This, however, would be anatomically difficult (a tremendous amount of photoreceptors, retinal neurons and optic nerve fibers would be necessary), and not economical (information about many objects would be conveyed concurrently to the higher visual centers, while essentially only one object may be perceived in a given moment). In the vertebrates with sharp vision, a much more convenient system is in operation, namely, only some part of the retina is specialized for detailed vision (area centralis). In this system the special reflex must be obviously provided to bring the image of the object on the area centralis and maintain the image in this position for a while. This is precisely the fixation reflex.

In some animals (e.g. in many fishes) the fixation reflex is executed exclusively by the appropriate eye movement (in animals with binocular vision by the conjugate movement of both eyes). On the other hand, in some animals (e.g. in many birds) this reflex is executed by head movement. In the majority of animals, however, both eye movement and head movement may contribute in the fixation reflex. In addition, movement of the body may be also occasionally involved. In this report, however, we will concentrate our attention mainly on the ocular component of the fixation reflex.

After perception of an object the return movement may immediately appear and then the fixation reflex will be referred to as *simple*. In other cases, the fixation is further maintained being nessesary for proper execution of a given "specific" response (see Żernicki 1968a). For example, after evaluation of the object as a prey, further fixation may be necessary for getting it. Such additional fixation will be called *secondary* and the fixation reflex reffered to as *complex*. The simple fixation reflex needs a further comment. As is well known, this reflex may be evoked by so called "neutral" stimuli. However, it may be also produced by some meaningful stimuli. For example, after evaluation of the object as the enemy, the animal may not fixate it further but will run away.

The fixation reflex is obviously only a part of reflex activity evoked by a given stimulus. It is usually associated with an accommodation reflex and in animals with binocular vision with the vergence reflex. Furthermore, the complex fixation reflex is usually a part of the specific response. For example, the complex fixation reflex may be associated with running to the food and eating it. Finally, the fixation reflex is associated with a considerable arousal response, which is manifested among others by a pupillary dilatation. The strength of the arousal response may be easily estimated in the simple fixation reflex to a neutral stimulus because then the specific response does not contribute in evoking arousal.

The fixation reflex is present only in an awake animal, but for its accurate recording the subject must be relatively restrained. Man may be easily restrained by appropriate verbal instruction. Due to this in the past the fixation reflex was almost exclusively studied on humans.

Recently the pretrigeminal cat, described by Moruzzi and his associates (Batini et al. 1959, see also Żernicki 1968b), has been extensively used for the investigations of the fixation reflex. After pretrigeminal brain stem transection, the cat may be restrained in the head holder while its isolated cerebrum remains awake. Due to the preservation of the visual input to the cerebrum and the main part of the oculomotor output (third and fourth cranial nerves) the vertical fixation reflex is present in such a preparation.

II. BEHAVIORAL PROPERTIES

Phases of fixation reflex. In the reflex three phases may be usually clearly distinguished. In *Phase I* the eyeballs direct themselves toward the object. This phase consists in one or a few saccadic movements (Fig. 1). The latency of the saccadic movement does not depend on its size, and it lasts 125—250 msec in man (Westheimer 1954a, Rashbass 1961) and 130—180 msec in the cat (Żernicki and Dreher 1965). On the

other hand, the velocity of the saccadic movement is positively correlated with its size. For 15° movement the mean velocity may reach 270°/sec in man (Robinson 1964, Yarbus 1965), 440°/sec in monkey (Fuchs 1967a), and only 125°/sec in the cat (Ebersole and Galambos 1969, Dreher and Kozak, in preparation).

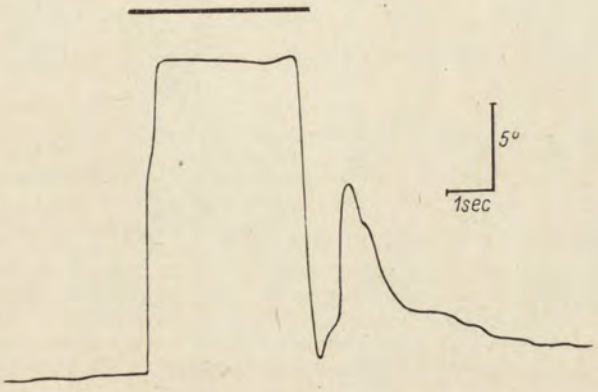


Fig. 1. Vertical simple fixation reflex in the pretrigeminal cat. As a stimulus (marked with a heavy line) 1 c/sec rotation of a white *X* shaped figure placed permanently on the black perimeter was used. The diameter of *X* figure was 12° and it was located 25° above the horizontal plane through the nodal point of the eye. The eye movements were recorded by a photokymograph with a technique developed by Dreher and Kozak (in preparation). A band of light was reflected by a small mirror attached to a light pulley, pivoting above the eye and connected with the conjunctiva of the eveball by a thread. Note two saccadic movements in the Phase I of the reflex

This considerable difference between primates and the cat in the velocity of the saccadic movements may be connected with the fact that in the cat the amplitude of these movements is usually much smaller. During immobilization of the head, the diameter of the fixation field is about 100° in primates and only 35°—40° in the cat. Probably due to this, in the cat isolated eye movements are rarely observed, and are usually accompanied by movements of the head and body. Such association is also manifested in the effects of stimulation (Hess 1954, Jung and Hassler 1959, Hassler 1960, Hyde 1965) and ablation (Dreher et al. 1965, Sprague and Meikle 1965) of neural structures involved in the fixation reflex.

During *Phase II* the fixation of the object is maintained. This phase consists of one or a number of unitary fixations (Fig. 1 and 2). In the latter case, the eyes fixate successively, with small saccadic movement, different points of the object (a given point may be fixated several times).

The duration of an unitary fixation must be satisfactory for perception processes. According to Keesey (1960) during fixation of the object by man visual acuity increases within 250 msec. The number of unitary fixations (and possibly also their duration) depends on the angular size

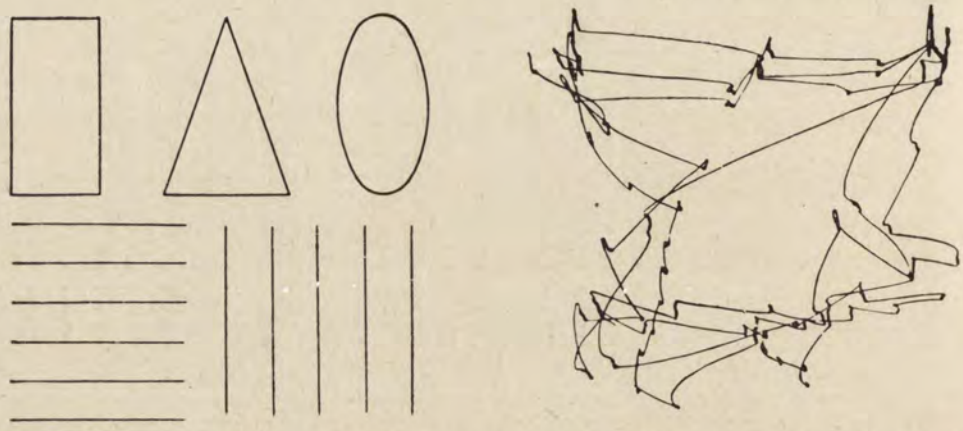


Fig. 2. Record of the eye movements in man during 20 sec spontaneous (without any instruction) inspection of the geometric figures. From Yarbus 1965

of the object, its complexity, and its possible movement. In the complex fixation reflex (see Chapter I) this phase consists of two subphases: primary and secondary. In the latter subphase the unitary fixations may be long-lasting and numerous. During inspection of an art picture, for example, the time of unitary fixation varies from 250 to 2000 msec (Yarbus 1967).

During a unitary perception the eyeballs perform slight movements. In man three types of movements are clearly distinguished: (i) high frequency (from 30/sec to 100/sec) tremor of amplitude from 10″ to 40″, (ii) slow drift from 5′/sec to 30′/sec, and (iii) saccadic movements of amplitude from a few minutes to about one degree (Ratliff and Riggs 1950, Barlow 1952, Ditchburn and Ginsborg 1953, Cornsweet 1956, Yarbus 1965). The last movements only are conjugate. Recently, during maintenance of fixation these three types of movements were also observed in the cat (Dreher and Kozak, in preparation). The high frequency tremor is probably due to some asynchrony in the activity of the motor units of the extraocular muscles. The slow drift and high frequency tremor seems to be necessary for long-lasting perception of the stimulus (Cornsweet 1956, Krauskopf 1957, Krauskopf et al. 1960, Ditchburn et al. 1959). We know that when the image of an object is artificially stabilized, after a few seconds man stops seeing it (Ditchburn and Ginsborg 1952, Riggs et al. 1953, Yarbus 1965). This is in accordance with the observation

that many neurons of the visual system react mainly to the appearance and disappearance of the stimulus ("on" "off" units). The small saccadic movements seem to have corrective meaning in the case when the drift movement moves the image away from the area centralis (Krauskopf et al. 1960, Yarbus 1965).

Phase III of the fixation reflex consists in a return movement.

In addition, in response to a neutral stimulus *Phase IV* of the fixation reflex was described in the cat (Żernicki and Dreher 1965). This phase is manifested in two different ways:

1. After the incomplete return movement the eyeballs are slightly inclined toward the object for a few seconds, or even minutes.

2. The return movement is followed by one or several after-fixations (Fig. 3). They are usually accompanied by searching movements.

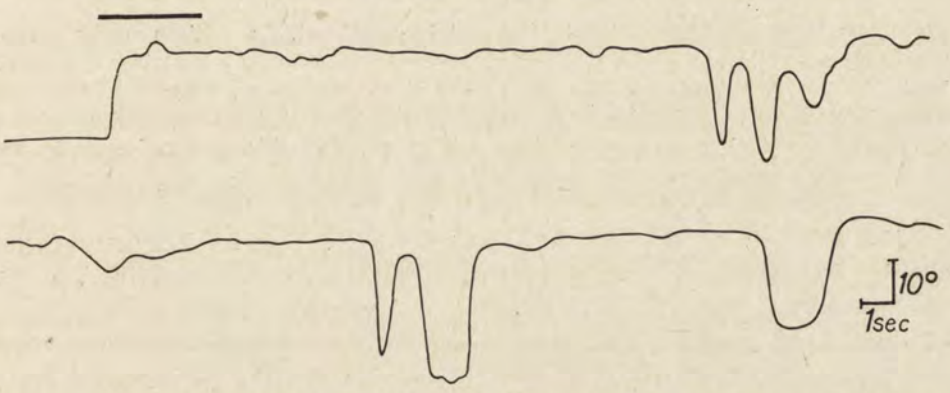


Fig. 3. The orienting fixation reflex with after-fixations (only the first after-fixations are shown). Denotations as in Fig. 1

Following reflex. When the object moves slowly and with a constant speed in the visual field, the phase of maintenance of fixation reflex consists in a following pursuit movement, which is only occasionally interrupted by small corrective saccadic movements. Such fixation reflex is called a *following* reflex (Fig. 4). It is interesting that even the neutral stimuli may be followed for several seconds or even minutes. The following reflex shows considerable adequacy when: (i) the velocity of an object is to 40°/sec in man (Dodge et al. 1930, Drischell 1968, Robinson 1965), to 45° in monkey (Fuchs 1967b), and from 5°/sec to 30°/sec in the cat (Dreher and Kozak, in preparation), and (ii) the frequency is up to 1.6 c/sec in man and 0.6. c/sec in the cat. Those observations in the cat seem to be in accordance with electrophysiological data showing that the optimal speed of movement for evoking the responses of neurons in visual cortex and in superior colliculi is usually from 0.5° to 20° (Hubel

and Wiesel 1962, Straschill and Taghavy 1967, Pettigrew et al. 1968, Sterling and Wickelgren 1969). When the movement of the followed object is predictable (e.g. sinusoidal), the position of the line of sight may slightly anticipate the position of the stimulus (Westheimer 1954b, Dallos and Jones 1963).

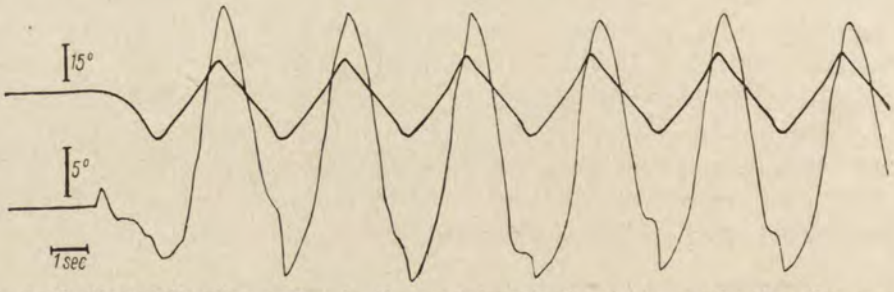


Fig. 4. Vertical following reflex in the pretrigeminal cat. As a stimulus the movement of the reflected 1° band of light moving against the perimeter was used. Both the movement of the stimulus (heavy line) and the movement of the eyes (light line) were recorded by a photokymograph. Note that the movement of the stimulus near its bottom position was not smooth and this was reflected in the eyeballs track

Habitutation of the simple fixation reflex. The habituation of the simple fixation reflex to a neutral stimulus was studied in the cat (Żernicki and Dreher 1965) and in the chimpanzee (Berkson and Fitz-Gerald 1963, Berkson 1965). In the cat after a few presentations of a stimulus with short-lasting (30—120 sec) intertrial intervals, the fixation reflex usually becomes abortive (see below), and after the following several trials disappears completely (Fig. 5).

It is interesting that simultaneously with habituation of the fixation reflex, the residual tonic fixation present after the return movement (Phase IV) becames gradually larger (Fig. 5). Due to this "summation" of the residual fixation the diminution of the amplitude of the fixation reflex produced by habituation may be partially compensated.

If after complete habituation of the fixation reflex a rest of 5 min is allowed, the spontaneous recovery is considerable (Fig. 5), and after a rest of 1 hr it is usually complete. However, when several sessions of habituation following each other at 1 hr intervals are conducted, chronic habituation of the fixation reflex is obtained.

Abortive fixation reflex. As was aforementioned, during the process of habituation in the cat the fixation reflexes may become abortive, i.e. the eye movements become unsatisfactory to bring the image of the object on the area centralis. It is possible that then such reflexes are satisfactory for perception (see next Chapter) because the appropriate

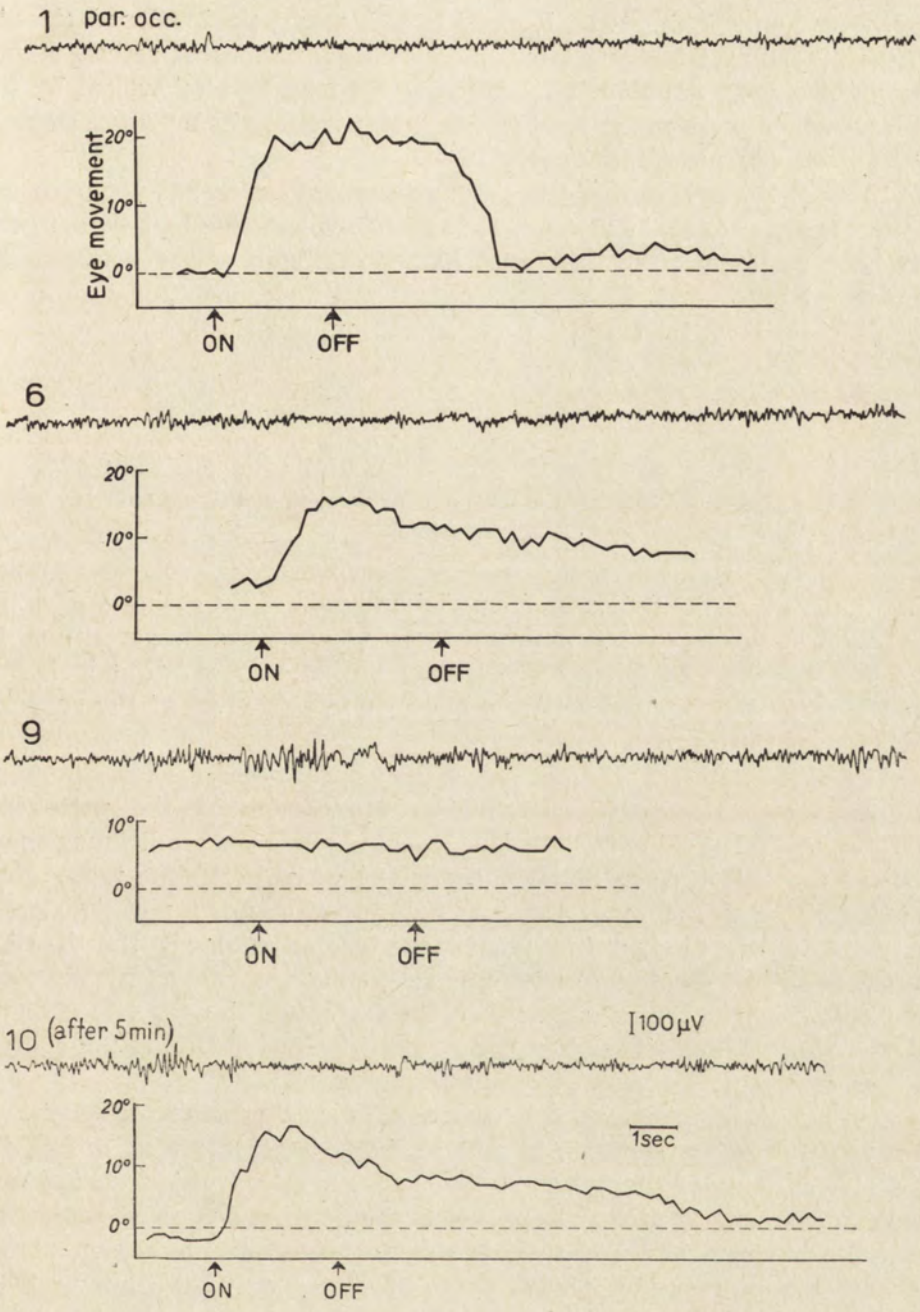


Fig. 5. Habituation of the fixation reflex and ECoG arousal to the rotation of *X* figure. For parameters of the stimulus see Fig. 1. Intertrial intervals 30 sec. The position of the eyeball before the application of any stimuli was taken to be zero level. The eye movements were filmed. From Żernicki and Dreher 1965

perceptual unit (Hebb 1949, Konorski 1967) might be developed already in the preceding trials and later activated by a peripheral retinal stimulation. However, the abortive fixation reflex may be also evoked by the stimuli which were never used in the past, particularly by small stationary objects (Żernicki and Dreher 1965).

In man, the presence of the abortive fixation reflex has not been experimentally proved. If present, it is probably less frequent than in the cat because in man the difference in the resolving power between the peripheral retina and the area centralis is much stronger (for data in cat see Chievitz 1889, Zürn 1902, Stone 1966, Donovan 1966).

III. PSYCHIC RESPONSES

First of all, the vision produced by the stimulation of the peripheral part of the retina should be considered. As we know introspectively, such vision is poor: we are aware of the presence of an object but we do not see it sharply and we cannot usually recognize it. It may be assumed that in man the stimulation of the peripheral part of the retina evokes the sensation of the object but is unsatisfactory to produce its perception. In the cat, however, peripheral vision may be better. According to Myers (1964), when the fixation reflex is absent (after removal of the superior colliculi), pattern vision is preserved.

The problem arises whether or not the central processes corresponding to the visual sensation (produced by stimulation of the peripheral part of retina) are involved in the evoking of the saccadic movement toward the object. Such involvement is suggested by (i) the rather long latency of the saccadic movement, and (ii) the well known fact that under narcosis (when the psychic phenomena are eliminated) the fixation reflex is absent. Then, however, this reflex may be evoked by the local application of strychnine sulphate on the surface of the superior colliculi (Apter 1946), which shows that the connections not involving the central processes in question are at least present (Fig. 6A).

During eye movement the image of the object obviously moves through the retina. During the saccadic movement, however, this is not perceived (saccadic suppression). The impairment of vision during saccadic movement is also present when the stimulus is so short-lasting that the blurring of the retinal image (suggested as the reason of the saccadic suppression by Dodge 1900, 1905) is excluded (Latour 1962, Volkmann 1962, Zuber and Stark 1966). Vision is also strongly reduced during 40—50 msec preceding the saccadic movement. The impairment of vision is accompanied by the strong reduction of the amplitude of the evoked potentials in the visual cortex (Gross et al. 1967, Michael and

Stark 1966, 1967, Marchiafava et al. 1967) and the impairment of the light reflex (Zuber et al. 1966). Holt (1903) has already claimed that during saccadic movement the treshold for vision is increased by central inhibition. More recently Sperry (1950) put forward the hypothesis of "corollary discharge" suggesting the inhibition of the visual system by the oculomotor system. Probably the neurons sensitive to movement, which are located in the tecto-pretectal region and visual cortex (see next Chapter), are inhibited. In this context it may be noted that in frogs and rabbits, in which fixation reflex is absent, the detection an analysis of movement take plays already in the retinal ganglion cells (Maturana et al. 1960, Barlow et al. 1964, Barlow and Levick 1965, Finkelstein and Grüsser 1965).

Let us turn to Phase II and Phase III of the fixation reflex. It may be assumed that the stimulation of the area centralis maintains the fixation of the object on the one hand, and evokes its perception on the other (Fig. 6). Furthermore, it is reasonable to think that the central processes corresponding to the perception of the object are involved in producing the return movement.

It may be also assumed that in the simple fixation reflex evoked by a meaningful stimulus and in the complex fixation reflex (see Chapter I) the central processes corresponding to the perception of the object are involved in the evoking of the specific response (Fig. 6 BC). In the complex fixation reflex the central processes for the specific response may contribute in the maintaining of the fixation.

IV. NEURAL PATHWAYS

Our knowledge on the arc of the fixation reflex is far from being satisfactory. In fact, this knowledge is mainly based on the effects of gross neural lesions, in which several links of the reflex arc may be impaired jointly. Therefore, our discussion will have a rather general character and we will not attempt to specify the neural pathways for separate phases of the fixation reflex.

The simple fixation reflex in the cat. There is clear evidence that in the cat the tecto-pretectal region and the visual cortex are directly involved in the arc of the fixation reflex. After ablation of the superior colliculi, the impairment of both the ocular and head component of the fixation reflex is dramatic: the fixation reflex in the vertical plane is absent and in the horizontal plane only occasionally present in the abortive form (Blake 1959, Myers 1964, Dreher et al. 1965, Sprague and Meikle 1965). In such animals the application of amphetamine (2 mg/kg

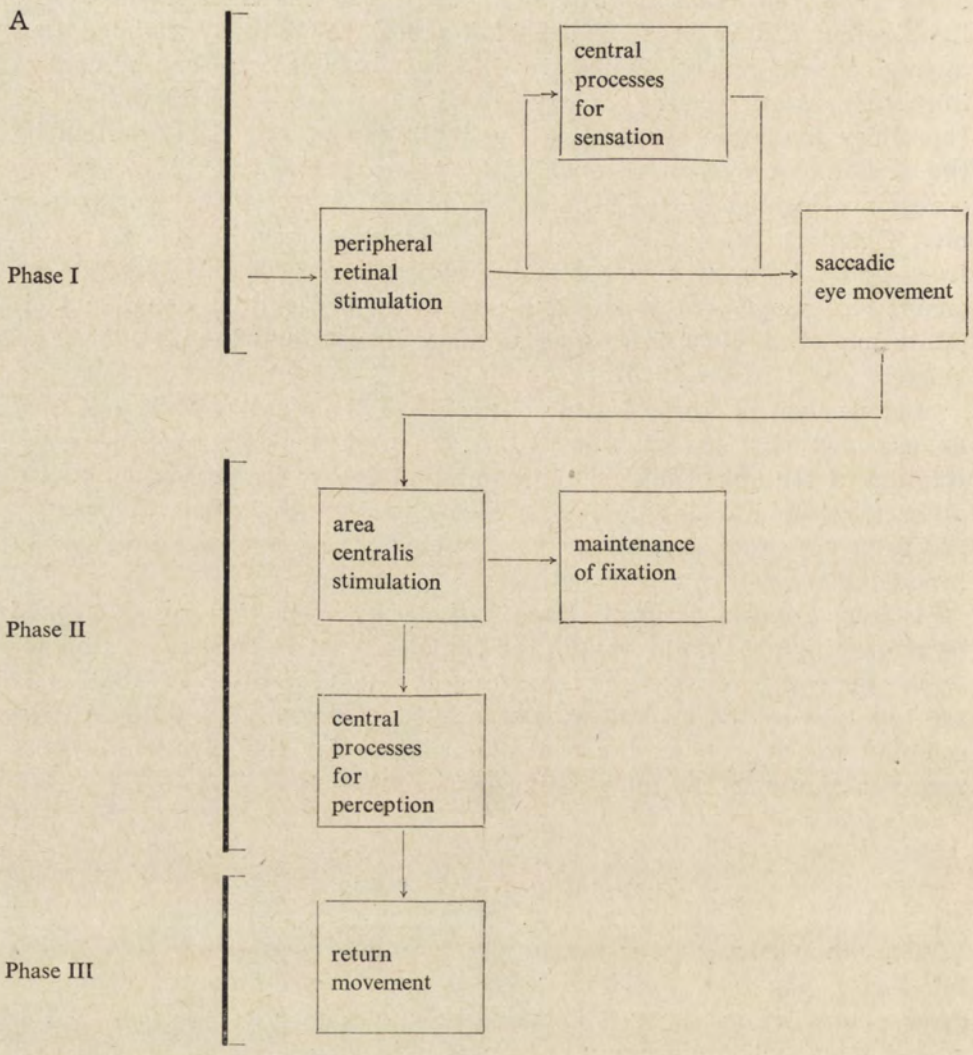
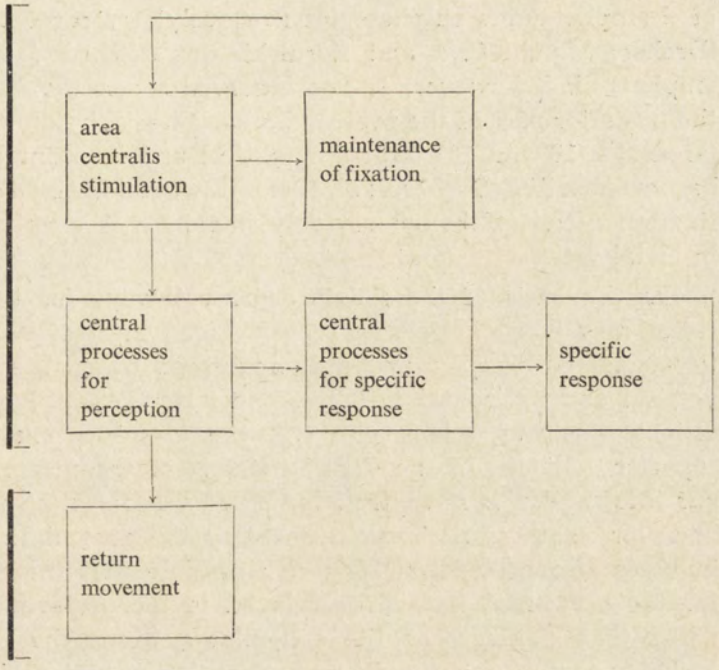


Fig. 6. Hypothetical diagram of the fixation reflex denoting the central processes corresponding to psychic responses (simplified). A, Simple fixation reflex to a neutral stimulus. B, Simple fixation reflex to a meaningful stimulus. C, Complex fixation reflex. In B and C Phase I of the reflex is not shown

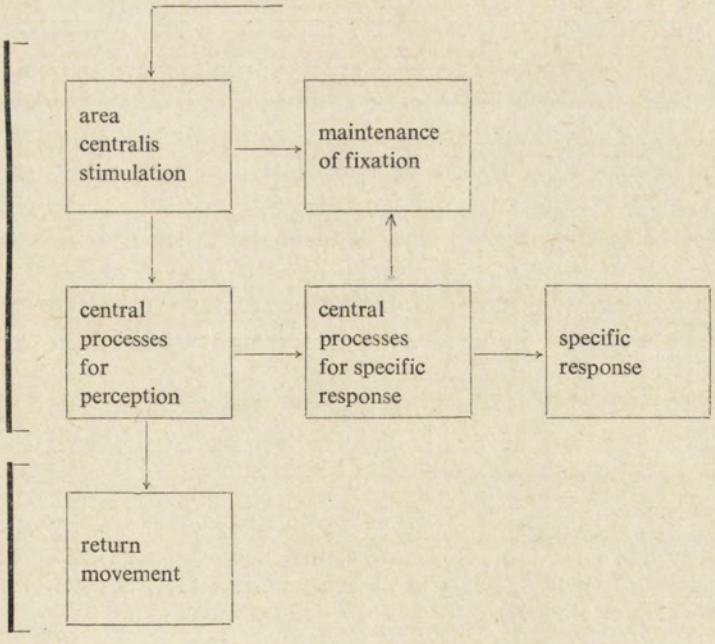
B



Phase II

Phase III

C



Phase II

Phase III

of d-amphetamine sulphate intravenously) improves the fixation reflex (Dreher, Marchiafava and Żernicki, unpublished data). This effect of amphetamine, however, is not observed when the lesion involves also the posterior part of the pretectal area. After ablation of the visual cortex (areas 17, 18 and 19) both the vertical and horizontal fixation reflexes become abortive (Dreher et al. 1965). However, in these cats the horizontal fixation reflex, although severely impaired, is clearly better than that in tectal cats.

On the basis of these data some pathways for the simple fixation reflex may be suggested. As seen in Fig. 7 the tectal and geniculato-cortico-tectal pathways may be distinguished which are common for both vertical and horizontal reflexes. The latter reflex, however, has an additional pathway which goes via the visual cortex but bypasses the superior colliculi. In the Fig. 7 the role of the pretectum, about which our information is not adequate, is not shown. It is reasonable to think, however, that the pathway denoted as the geniculato-cortico-tectal one involves also pretectum. It is also possible that the "private" pathway for the horizontal fixation is relayed in the pretectum. It may be also noted that similarly as the collicular neurons the pretectal cells are sensitive to movement and its direction (Harutiunian-Kozak et al. 1968b), and the stimulation of the pretectum produces eye movements (Hyde and Eason 1959, Hyde 1960ab).

It is interesting to consider what the differences are in the role of the tecto-pretectal and cortical links of the fixation reflex. In this respect some functional differences between these structures should be noted:

1. Although the tecto-pretectal area is more important for the fixation reflex, the occipital cortex is more important for vision. In the occipital cats the visual acuity is not impaired (Smith 1938, 1939, Smith et al. 1940) but pattern vision and the perception of movement of a visual object are clearly affected (Kennedy 1939, Winans 1967) [1]. On the other hand, in tectal cats pattern vision is essentially undisturbed (Myers 1964). Some impairment of visual discrimination in such animals (Blake 1959) seems to be rather due to the deficit in spatial orientation (Schneider 1967). In pretectal cats, however, the impairment of brightness discrimination was reported (Thompson et al. 1963).

2. The prevalence of the representation of the area centralis over the periphery of the retina is stronger in the visual cortex than in the

[1] It should be noted that in the cat some visual input from the lateral geniculate body and from the posterolateral thalamic complex is directed to the "non-visual" cortex (Doty 1958, Buser et al. 1959, Vastola 1961, Bignall et al. 1966, Bignall 1967, Berkley et al. 1967).

tectal region (Talbot and Marshall 1941, Marshall and Talbot 1942, Apter 1945). This may partly explain the presence of only the abortive fixation reflex in occipital cats.

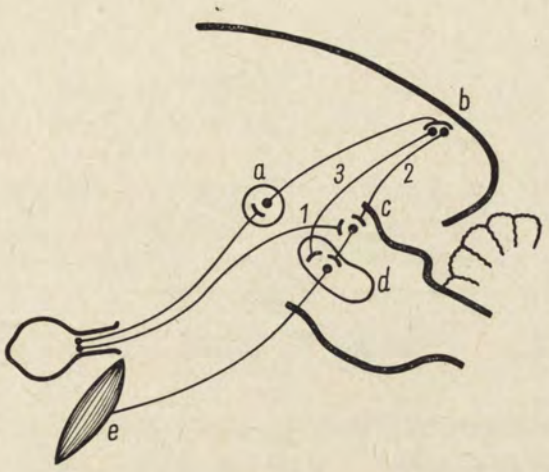


Fig. 7. Schematic diagram illustrating the recognized pathways of the simple fixation reflex in the cat. a, lateral geniculate; b, visual cortex; c, superior colliculus; d, oculomotor nuclei; e, eye and head muscles; 1, tectal loop; 2, geniculato--cortico-tectal loop; 3, geniculato-cortical loop for horizontal fixation. From Dreher et al. 1965

3. The receptive fields of the neurons in the visual cortex are usually smaller than in the tecto-pretectal area and have a more complex inner organization, which is based on the antagonistic "on" and "off' elements (Hubel and Wiesel 1959, 1962, 1965). In consequence, these neurons may give information about the exact position of the stimulus, which is necessary for the adequate fixation reflex.

4. In contrast to the neurons of the visual cortex, most of the tectal and pretectal neurons react exclusively to movement and show directional sensitivity (Hubel and Wiesel 1962, 1965, Baumgartner et al. 1964, Marchiafava and Pepeu 1966, Straschill and Taghavy 1967, Wickelgren and Sterling 1967, McIlwain and Buser 1968, Ganz et al. 1968, Harutiunian-Kozak et al. 1968ab, Pettigrew et al. 1968, Sprague et al. 1968). The majority of tectal neurons react exclusively to the movement away from the point of visual field corresponding to the area centralis (Straschill and Hoffman 1968, Sterling and Wickelgren 1969). It may be suggested that the tecto-pretectal area is more concerned with an answer to the question "where is the stimulus", while the visual cortex with an answer

to the question "what is the stimulus" (see Schneider 1967). However, Wickelgren and Sterling (1967, 1969) reported that after ablation of the occipital cortex the directional sensitivity of collicular neurons disappear and the number of cells responding exclusively to movement is strongly reduced.

Table I

The syndrome of fixation time increase in cats with frontal oculomotor or prefrontal ablations (from Dreher and Żernicki 1969)

Group	Mean duration of fixation (in seconds)	Percentage of cats with after-fixations	Mean resistance to habituation (in trials)
Control N = 11	6.9	18	23.3
Oculomotor N = 9	12.6	55	84.7
Prefrontal N = 5	11.0	100	60.8

When in the cat the frontal oculomotor cortex or prefrontal cortex is removed the fixation reflex is not impaired but clearly enhanced (Jeannerod et al. 1965, Jeannerod et al. 1968, Dreher and Żernicki 1969). This is manifested by prolonged fixation, the presence of after-fixations, and increase of the resistance to habituation (Table I). It may be concluded, therefore, that the frontal lobes inhibit the fixation reflex. Possibly this inhibition takes place in the tecto-pretectal region, to which there is a clear frontal projection (Sprague 1963).

Further information on the fixation reflex arc is supplied by the observation that in the decerebrate cat the fixation reflex is absent (Żernicki et al. 1970). This may be explained in two ways: (i) The tectal pathway for the fixation reflex may operate only on the background of some arousal, which is poor in the decerebrated animal (Jouvet 1962, Villablanca 1966, Żernicki et al. 1969). In fact, in such an animal the abortive fixation reflex may be evoked following strong electrical stimulation of the midbrain reticular formation. It may be also noted that on the background fo the arousal evoked by MRF stimulation, the excitability of the neurons in the lateral geniculate body and in the visual cortex is increased (Nakai and Domino 1968, Fuster 1969). (ii) Apart from the tecto-pretectal region and visual cortex, other structures are directly involved in the fixation reflex arc. This might be the caudate nucleus (Thompson 1959, Laursen 1963).

The simple fixation reflex in primates. Both in man and in monkey bilateral ablation of the whole visual cortex results in total abolition of the fixation reflex (Holmes 1938, Pasik et al. 1959). This is associated with total blindness in man (Holmes 1938), and with almost total blindness in monkey in which only luminous flux discrimination and discrimination between continuous and intermittent light were observed (Marquis 1935, Klüver 1937, 1941, 1942, Anderson and Symmes 1969). However, in monkey after bilateral ablation of only area 17 the fixation reflex to moving stimuli is partially spared (Denny-Brown and Chambers 1955, Humphrey and Weiskrantz 1967). As we know such ablation is followed by a full degeneration of the lateral geniculate body. Therefore, for the fixation reflex to at least moving stimuli the extrageniculatal input to areas 18 and 19 may be important.

On the other hand, in monkey after ablation of the superior colliculi the impairment of the fixation reflex is equivocal. Some authors (Denny-Brown 1962, Pasik et al. 1966a) did not observe any impairment. On the other hand, in animals with even incomplete collicular ablations Anderson and Symmes (1969) found the absence of the fixation reflex to weak stimuli and the reduction of the spontaneous ocular activity. In light of some clinical data (see Holmes 1938) that the phase of maintenance of fixation is impaired after the lesions of the occipito-tectal pathways, it is possible that the occipital projection for the fixation reflex is partially mediated by the superior colliculi. Some role of the superior colliculi in the fixation reflex in monkey is also suggested by the observation that similarly as in the cat the collicular neurons are very sensitive to movement (Humphrey 1968). However, they show no directional sensitivity. The deficit in vision in tectal monkeys seems to be limited to the impairment of discrimination of speed of movement (Anderson and Symmes 1969).

In contrast to the lesions of superior colliculi, those of the pretectum produce a serious impairment of the fixation reflex in monkey and the same seems to be true for man (Bender and Schanzer 1964, Pasik et al. 1966b). This suggests that in primates the cortical projection for the fixation reflex is relayed in the pretectum. In pretectal monkeys the pattern vision seems to be also impaired (Anderson and Symmes 1969).

Finally, both in monkey and in man the fixation reflex is severely impaired after lesions of the caudate nucleus (Mettler and Mettler 1942, Starr 1967), and conversely increased after frontal lesions (Gowers 1879, Holmes 1938, Henderson and Crosby 1952, Teuber 1964). It may be noted that in monkey the abundant frontal projection to the tectal region was described (Astruc 1964, Kuypers and Lawrence 1967).

The simple following reflex. After lesions of both the tecto-pretec-

tal region and the visual cortex the impairment of the fixation reflex is accompanied by a comparable impairment of the following reflex. However, there is some evidence that the reflex arc of the latter is to some degree specific:

1. In human patients with lesions of the parietal or frontal cortex (Gassel and Williams 1963, Rodin 1964) and in monkey with lesions of the area 17 (Humphrey and Weiskrantz 1967) the pursuit movements may disappear while the saccadic movements are preserved, and conversely after lesions of caudate nucleus saccadic movements may disappear while pursuit movements are present (Starr 1967).

2. In human infants saccadic movements are observed already a few days after birth but the pursuit movements only three months later (Gessell et al. 1949).

3. Rashbass (1961) observed that in man after intravenous injection of small dose of sodium amytal the pursuit movements disappear while the saccadic ones are preserved.

4. Bizzi (1968) found that in the frontal eye field of waking rhesus monkey two closely intermingled populations of cells exist. The cells of the first type respond during saccadic movements, while the cells of the second type respond during pursuit movements or during the phase of maintenance of fixation.

5. In some mammals different muscle fibers for the saccadic and pursuit movements were described (Hess 1961, Hess and Pilar 1963, Dietert 1965, Bach-y-Rita and Ito 1966). The fibers of the first type have a single end-plate and are characterized by a high speed of depolarization. These fibres can contract with a frequency up to 450/sec. The fibers of the second type have many end-plates and are characterized by a small speed of depolarization and a small frequency of contraction (no more than 15—20/sec). The muscle fibers are supplied with nerve fibers of different diameter (Pilar and Hess 1966) and of different speed of conduction (Bach-y-Rita and Ito 1966).

Habituation of the simple fixation reflex. In intact animal the resistance to habituation of the fixation reflex is positively correlated with its intensity. In cats with occipital or frontal lesions both the change of the intensity of the fixation reflex and the change in its resistance to habituation were observed (Dreher et al. 1965). However, the latter symptom was more pronounced. In occipital cats the abortive, though still of considerable size, fixation reflex disappeared already after a few presentations of the stimulus. On the other hand, in cats with frontal oculomotor or prefrontal lesions the resistance to habituation of the moderately enlarged fixation reflex was dramatically increased (Table I).

The rapid habituation of the fixation reflex in occipital cats is in

accordance with recent electrophysiological observations that the habituation of the responses of neurons in the superior colliculi and pretectal region is fast (Horn and Hill 1966, Strashill and Taghavy 1967, McIlwain and Buser 1968, Harutunian-Kozak et al. 1968ab, Humphrey 1968, Sprague et al. 1968), while the habituation of the unitary responses in the lateral geniculate body and in the visual cortex is slow (Hubel and Wiesel 1959, 1962, Kozak et al. 1965, Ganz et al. 1968).

The complex fixation reflex. This reflex may be considered as the simple fixation reflex enriched by the secondary fixation (see Chapter I and III). The neural mechanisms of the simple component is obviously common in different complex fixation reflexes and it has been already discussed. In addition, we may suppose that there exists a common neural mechanism subserving the smooth trasformation of the primary fixation into the secondary one. On the other hand, in particular reflexes the mechanism of the secondary component must be different. Secondary fixation may be part of an alimentary reflex (the animal observes the food), or part of a defensive reflex (the animal observes the enemy), etc.

V. REFLEXES TO BE DISTINGUISHED

1. Optokinetic reflex (optokinetic nystagmus). In contrast to the following reflex the optokinetic reflex is not evoked by the movement of a given object but by the movement of the whole visual field or a considerable part of it. In consequence, the optokinetic reflex is present also in those animals in which the retina is not specialized for detailed vision, for example in the rabbit. The arc of the optokinetic reflex seems to be quite different from that of the fixation reflex. The optokinetic reflex is not impaired by visual cortex ablation (Smith 1938, 1939, Smith et al. 1940, Smith and Bridgman 1943, King and Marchiafava 1963), and is still present after superior colliculi lesions (Urbaitis and Meikle 1968).

2. Movement of eyes and head evoked by non-visual stimuli (for example, by auditory stimuli). Such movement, however, may be followed by the fixation reflex. For example, the sound of steps evokes the orienting movement of the eyes and head toward the source of stimulation (this is not a fixation reflex), and when the image of a man appears on the periphery of the retina, the fixation reflex occurs.

It should be noted that in the cats with lesions of superior colliculi not only the fixation reflex is impaired but also directional responses to the stimuli of other modalities. Such impairment was observed to auditory stimuli (Sprague and Meikle 1965, Dreher, Marchiafava and Żernicki, unpublished data), and to tactile stimuli (Sprague and Meikle 1965). Moreover, in the cat Jassik-Gerschenfeld (1965) found a convergence of infor-

mation from different sensory modalities in an efferent tectal neuron, and according to Horn and Hill (1966) the same is true for a rabbit.

3. Eye and head movement initiated voluntarily. For example, the movement to the order "look at right", or to the order "look for the pencil on the table". Such movement, however, may be followed by the appropriate fixation reflex. For example, looking for the pencil may be followed by its fixation. There is some evidence obtained in man that voluntarily initiated eye movements are impaired by the lesions of the frontal oculomotor cortex (Gowers 1879, Holmes 1938, Teuber 1964).

VI. SUMMARY

1. In the fixation reflex three phases may be distinguished. Phase I consists in a saccadic movement toward the object. During Phase II the fixation of the object is maintained; in this time one or a number of unitary fixations occur. Phase III consists in the return movement.

When the object moves slowly and with a constant speed in the visual field, Phase II essentially consists in a following pursuit movement. Then the fixation reflex is called *following*.

2. When directly after the perception of the object the return movement appears, the fixation reflex is called *simple*. On the other hand, when the fixation is further maintained, the fixation reflex is called *complex*.

3. For the fixation reflex in the cat, two comparable in importance pathways may be distinguished: tectal and geniculato-cortico-tectal. The latter pathway is responsible for the adequate reflex. On the other hand, in primates the geniculato-cortico-pretectal pathway seems to be essential for the fixation reflex. Both in the cat and in primates the fixation reflex is inhibited by frontal lobes.

4. The fixation reflex should be distinguished from: (i) the optokinetic reflex, (ii) the movements of eyes and head evoked by non-visual stimuli, and (iii) the eye and head movements initiated voluntarily.

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Lecture delivered at the scientific session held in commemoration of the 50th anniversary of the Nencki Institute

December 1968

ELECTRICAL STIMULATION AND STEADY POTENTIAL SHIFTS IN PREFRONTAL CORTEX DURING DELAYED RESPONSE PERFORMANCE BY MONKEYS

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Our knowledge of the function of the frontal lobes has been derived almost exclusively from findings of behavioral impairments in brain-damaged subjects. In monkeys, ablations of the dorsolateral segment of prefrontal cortex have been found to result in severely and permanently impaired performance on the delayed response (DR) task (Brutkowski 1965). However, the findings from these investigations have not lent themselves to clear interpretations of the functional role of prefrontal cortex, because DR is a complex task which includes: exhibition of the cue that indicates the location of the reward, a delay period, the animal's instrumental response, and delivery of the reinforcement. The locus and crucial time of implication of prefrontal cortex in the DR task has been specified more clearly by applications of electrical stimulation of limited duration during discrete portions of the DR trial (Stamm 1969). Monkeys, whose prefrontal cortex ipsilateral to the responding hand had been ablated, continued to respond correctly when electrical stimulation was applied across the midportion of principal sulcus of the intact hemisphere during the intertrial interval or the early period of cue presentation. However, current applications of the same strength when applied during the first few seconds of the delay severely disrupted correct performance. Stimulation during the final second of cue presentation or during the later portion of the delay lowered response scores slightly, to levels of 70% to 85% correct. Stimulus applications to other

portions of dorsolateral frontal cortex yielded varying behavioral results.

An experimental technique which might provide more direct evidence of the specific involvement of prefrontal cortex in the DR task is the recording of electrocortical activity, including shifts in steady cortical potentials, during DR performance by monkeys with intact brains. In experiments of intersensory electrocortical conditioning (Rosen and Stamm 1966), conditioned surface-negative and -positive steady potential (SP) shifts have been obtained from auditory and visual cortex in monkeys during the different components of the conditioning procedure. These results support the conclusion stated by O'Leary and Goldring (1964) that surface negative cortical shifts are indicative of increased excitation of the underlying neuronal elements. Consequently, the technique of recording steady cortical potentials was applied in the present experiment in order to evaluate the significance of localized changes in cortical excitation in relation to performance on the DR task. Since this task requires sensory, motor, and mnemonic functions, the electrical activity was examined in occipital, precentral, and prefrontal cortical areas.

The method of electrocortical stimulation during DR performance was extended in the present experiment to monkeys with intact brains. The findings with these two techniques yielded corroborative results of impaired performance and of cortical steady potential shifts, respectively, during specific portions of the DR trial. We found it possible, moreover, to apply these techniques to problems of brain function which have thus far not been extensively investigated, such as interhemispheric differences and hemispheric functions in relation to transfer between the responding hands.

TESTING APPARATUS

During experimental testing the monkey was placed in a portable restraining chair (Fig. 1). This chair had two adjustable horizontal shelves which fitted around the monkey's abdomen and around its neck. Molded plastic shields were placed around its head so that the subject could not reach the electrical plug or the connecting cable at its head, but had a clear view of the testing panel. A cuff, which was attached by a chain to the abdominal shelf, was tied to the wrist of the monkey's non-preferred arm. The chair was placed securely in front of a vertical panel in which two circular display windows, 3.5 cm in diameter, were mounted at the subject's eye level, with 6.5 cm between their centers. Colored fields or white patterns could be projected on each window. In front of each window was a transparent plastic disk which, when pressed lightly,

activated a microswitch. Two transparent cups, 16 cm apart, were mounted beneath the display windows.

Fig. 1. Monkey in the restraining chair. Note: chain attached to monkey's right wrist and the plastic head restrainers

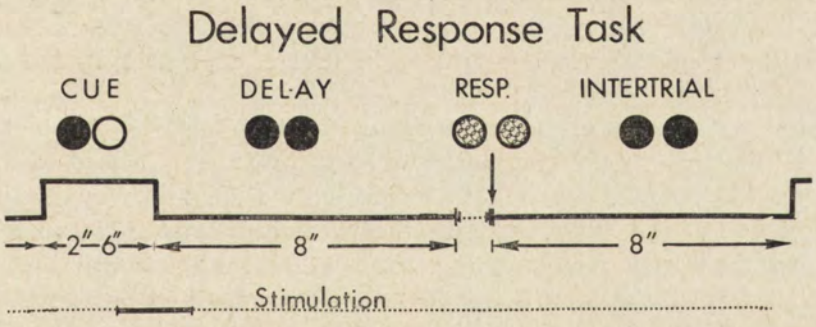

Fig. 2. Schematic representation of the delayed response (DR) trial. During cue presentation one display window receives white illumination and at end of delay period both windows are illuminated with blue light. Stimulation with 2 sec trains may be applied during any portion of the trial

On the DR task (Fig. 2) the cue was presented as a bright white field in either the left or right window, generally for two seconds. This was followed by an 8 sec delay period when both windows remained darkened after which blue fields were projected on both windows. When

the subject then pressed on either window the illumination was extinguished for an 8 sec intertrial interval. The correct response, a press to the window on which the cue had been presented, resulted in delivery of a 45 mg dextrose pellet to the food cup beneath the correct window and 2 sec of white illumination of that cup from the rear. On successive trials the cue was presented in the left or right window according to a random schedule, modified so that in every block of 10 trials each side was correct five times. Dim overhead illumination was provided throughout each testing session.

ELECTRICAL STIMULATION OF PREFRONTAL CORTEX

Subjects and electrodes: Four young monkeys (*Macaca speciosa*) served as subjects. The stimulating electrodes consisted of stainless steel spheres, about 0.5 mm in diameter, which were mounted on a thin polyethylene sheet. Each assembly contained 4 to 8 electrodes which were arranged in two rows with 10 mm distance between adjacent points. The wires from the electrode points were brought together in a cable and soldered to an Amphenol connector. During surgery, the skull was opened with rongeur, the dura was cut, and the assemblies were placed symmetrically on dorsolateral prefrontal cortex, so that the electrode points straddled the principal sulcus. The two Amphenol connectors were tied to screws over the occipital bones and cemented to the skull. After placement of the electrode assemblies the dura was sutured over the polyethylene sheets, the skull openings were covered with stainless steel screening, and the fascia and skin were sutured in layers, so that only the plugs protruded from the skin.

Preliminary training: During preliminary training each subject was adapted to sitting in the chair and its hand preference was determined by presenting peanuts when both hands were free. The monkeys were then trained on the DR task, with the preferred hand, first with zero delay and then with gradually increasing delay periods, until they responded at 80% correct on 8 sec DR. Surgery was then performed and training continued until the monkey responded at 85% correct on the task during three successive sessions of 120 trials each.

Prefrontal stimulation during the delay period: Stimulation was with a Grass S4 square wave stimulator, a stimulus isolation unit, and a constant current regulator. Bipolar stimulation, consisting of 2 sec trains of 1 msec pulses at the rate of 50 pulses per sec was applied across the middle portion of the principal sulcus of frontal cortex contralateral to the responding hand. At first the stimulus train started 1 sec before the start of the delay period of each trial and the current strength was in-

creased during blocks of 10 trials until performance scores dropped to near chance level. During the subsequent sessions this current strength was applied for 100 trials (except for the first and last 10 trials) and the onset of stimulus application was shifted after each 10 trial block (see Fig. 2). For every monkey one pair of electrode points was found which, when stimulation was applied through it, yielded the results illustrated by Fig. 3 and 4. For each monkey correct performance was markedly

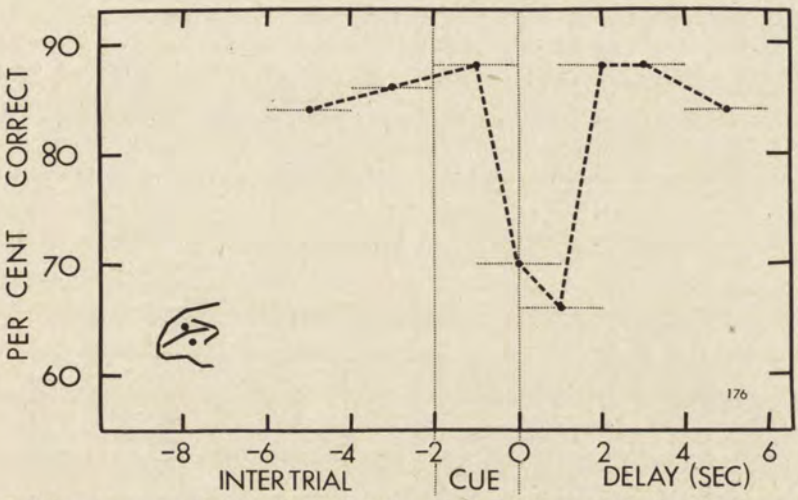

Fig. 3. Performance on 8 sec DR by S 176 with 2 sec trains of stimulation at 4.0 ma applied across prefrontal electrodes (location shown by insert). The time scale is with reference to start of delay period. Horizontal lines indicate periods of stimulation

disrupted when the stimulus train occurred during the first second of the delay. However, with stimulation during the subsequent portion of the delay period correct responses remained at or only slightly below criterion level. The results indicate individual differences with regard to the duration of the early delay period (range of 1 to 6 sec) when stimulation disrupted correct performance and with regard to the performance level during the later delay period, which was between 80 and 90% correct. The present results are in agreement with the earlier findings (Stamm 1969) that the effect of stimulation with constant stimulus parameters is a function of the period of stimulus application during the DR trial, with maximum disruption of correct performance occurring only when the stimulus is applied during the first few seconds of the delay.

Prefrontal stimulation during cue presentation: With 2 sec of cue presentation all monkeys responded at criterion level when the stimulus train terminated before the final second of the cue. In order to ascertain whether the effect of stimulation was time-locked to the onset of the

cue or was related to the start of the delay period, two monkeys were systematically tested with cues of 2, 4 and 6 sec duration. The results, as shown by Fig. 4, indicate that for each of these cue durations performance remained near criterion level with stimulation that terminated one sec before termination of the cue, while performance became maximally disrupted when stimulation began during the final second of cue presentation. Performance scores appeared to be a function of cue duration only when the stimulus train coincided with the final two seconds of the cues, when the mean response scores for the two subjects were 58%, 63%, and 73% correct, respectively, with cues of 2, 4, and 6 sec duration. This finding would indicate that presentation of the cue for several seconds before the onset of stimulation provides the monkey with sufficient information so that the subsequent stimulus will be less effective in disrupting correct performance. The higher performance score for simultaneous onset of the delay and the stimulus with 6 sec cue presentation was found only for Monkey 124 (Fig. 4), and we have no explanation for this unexpected result.

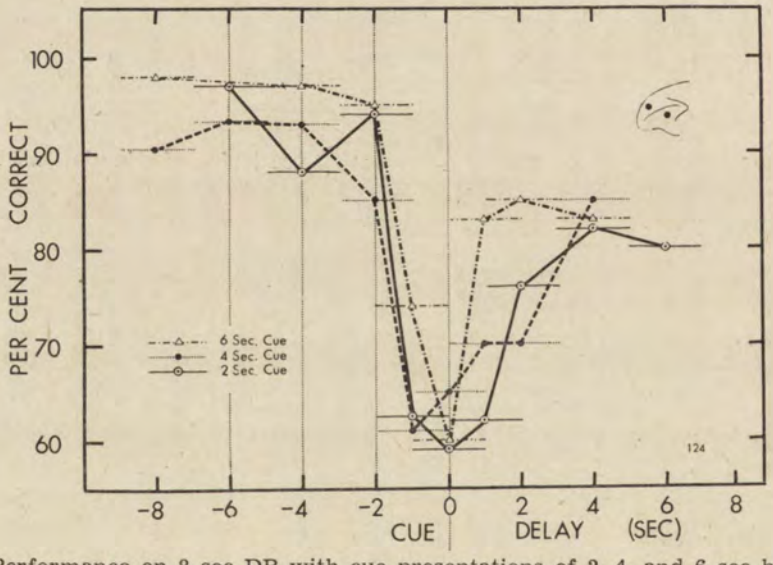

Fig. 4. Performance on 8 sec DR with cue presentations of 2, 4, and 6 sec by S 124. Stimulation with 2 sec trains at 5.5 ma, applied across left prefrontal electrodes (locations shown by insert). The time scale is with reference to start of delay period. Horizontal lines indicate periods of stimulation

Transfer of responding hand: Two monkeys which had received extensive training with the right (preferred) hand were subsequently tested on the DR task with their non-preferred hand and they rapidly reattained the 90% criterion of correct responses. Stimulation was then applied

through the same electrode points in the left prefrontal cortex which had previously been found to affect response scores. This resulted in the same changes in performance scores as had previously been obtained when the preferred hand was used (Fig. 3, 4), i.e., there were no appreciable differences in correct response scores for each period of stimulus application between testing with the right and left hands. When stimulation was applied through symmetrically located electrode points in right prefrontal cortex, correct performance remained unimpaired with current strengths as high as convulsive threshold, during testing with either the right or left hand. Replication of the testing procedure with stimulation through other electrode points generally had the same effects on DR performance regardless of the responding hand. These results would indicate that response scores on the task can be affected only by stimulation of cortex contralateral to the preferred hand. Ipsilateral prefrontal cortex does not appear to be essential to correct DR performance.

CORTICAL STEADY POTENTIAL SHIFTS

Subjects and electrodes: Four monkeys (*Macaca speciosa*) were trained at the DR panel until they responded at 90% correct on the 8 sec DR task with 3 sec of cue presentation. Silver-silver chloride nonpolarizable electrodes, of similar construction as those described by Rowland (1968), were then surgically implanted in several cortical structures. Each electrode was constructed of a small glass tube (8 mm diameter, 10 mm long) which was drawn at one end into a capillary shaft 1—2 mm in diameter. The tube was filled with a saline-agar gel into which a coil of fine silver wire (0.10 gauge) that had been coated with silver chloride was inserted. The tube was sealed at both ends with dental cement and coated with vinyl insulation. From the wide end of the tube emerged a silver wire which was continuous with the coil. At the time of surgery the capillary end was cut to the desired length so that the resulting electrode tip consisted of a circular section of saline-agar gel. Pairs of electrodes were placed bilaterally in frontal, premotor, posterior parietal, and lateral occipital cortex. One electrode of each pair was placed on the pial surface and the other in adjacent underlying white matter, with a 5—10 mm separation between tips. The principal sulcus was gently opened and the frontal surface electrode placed on cortex in the posterior third of the depth of the sulcus. All electrodes were fixed on the skull by means of stainless steel screws and dental cement. The electrode leads were soldered to points on Amphenol connectors which were cemented to the skull. Fascia and skin were sutured above the resulting mound of cement.

Recording apparatus: The shielded leads from the Amphenol connectors were connected to DC preamplifiers of a polygraph (Grass Model 5) which was located outside the testing chamber. Outputs from the power amplifiers of the polygraph were led, via differential amplifiers, to a seven-channel FM magnetic tape recorder (Honeywell, Model 7600). Information concerning cue presentation and the DR response was also stored on the tape. The data stored on the tape were subsequently fed into a computer of average transients (CAT, Model 1000) and variance computer (Bio-Medical Instruments, Model 204).

Characteristic patterns of SP shifts: Three weeks after surgery DR testing was resumed with ECG recordings obtained throughout the testing session. Polygraph recordings from cortex contralateral to the responding hand (Fig. 5) revealed surface negative SP shifts from prefrontal

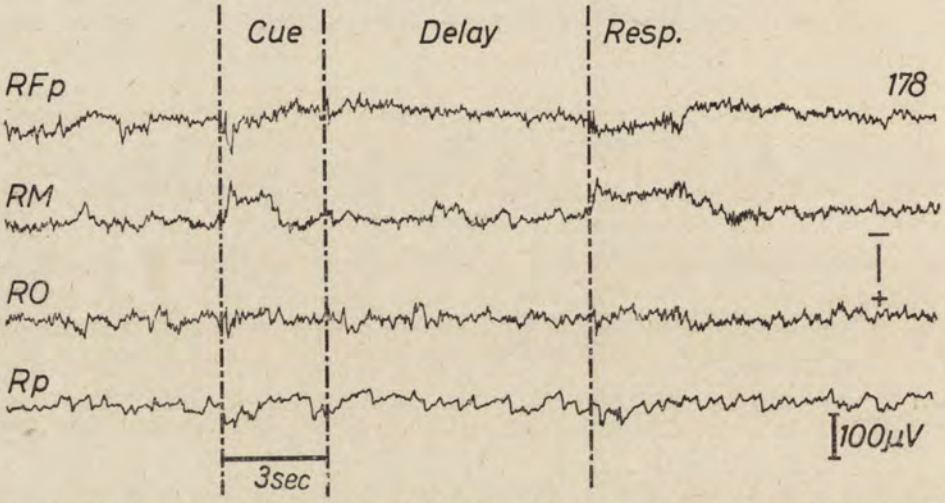

Fig. 5. Bipolar ECG traces with surface and depth nonpolarizable electrodes in right (R) hemisphere. Fp — principalis region of frontal, M — premotor, O — lateral occipital, P — parietal cortex. Recordings obtained during 8 sec DR performance. Calibration as indicated. Surface negativity upward

cortex during the end of cue presentation and the beginning of the delay period with a magnitude of 25—50 μV with reference to the pretrial level. A second prefrontal negative wave of 50 μV was recorded subsequent to the instrumental response, i.e., during the reinforcement period. The traces from premotor cortex showed 50—100 μV surface negative waves whenever the subject pressed the display button, i.e., during cue presentation, the delay, and the response periods. From occipital cortex evoked responses were recorded in relation to onset and offset of the cue and reinforcement lights. These responses generally were of 20 to 40 μV mag-

nitude and of less than 1 sec duration. SP shifts from parietal cortex were not clearly associated with events in the DR trial.

Averages of the ECG data were obtained for blocks of 40 trials by triggering the CAT sweep at the onset of the cue with the sweep rate set at 16 msec per address, so that each average was computed for an approximately 16 sec period. As can be seen by Fig. 6, the averaged

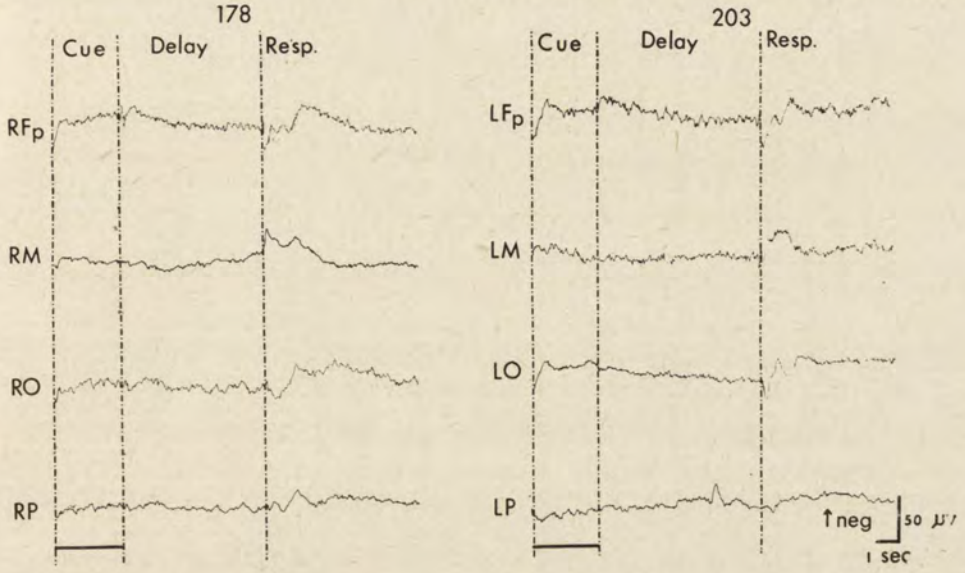

Fig. 6. Averaged ECG traces during 8 sec. DR task for a left handed (178) and a right handed (203) monkey. Averages are for 40 trials of surface to depth bipolar recordings of activity in prefrontal principalis (Fp), premotor (M), occipital (O), and parietal (P) cortex. The analysis sweep was triggered at onset of the cue. Calibration as indicated. Surface negativity upward

shifts in frontal and motor cortex correspond to those observed in the polygraph data, except that the monkey's responses during cue presentation and the delay interval were not reflected in the averaged results, since these occurred at random. Averaged responses from occipital cortex showed negative waves during presentation of the cue and reinforcement lights. No consistent patterns were obtained from parietal cortex.

SP shifts as a function of correct performance: The magnitude of the negative SP shift from prefrontal cortex appears to be related to the rates of correct and incorrect instrumental responses. For one monkey SP shifts were averaged for blocks of thirty trials when performance scores were 68% and 98% correct. As seen by Fig. 7, there were no differences in averaged SP shifts from premotor cortex between these blocks

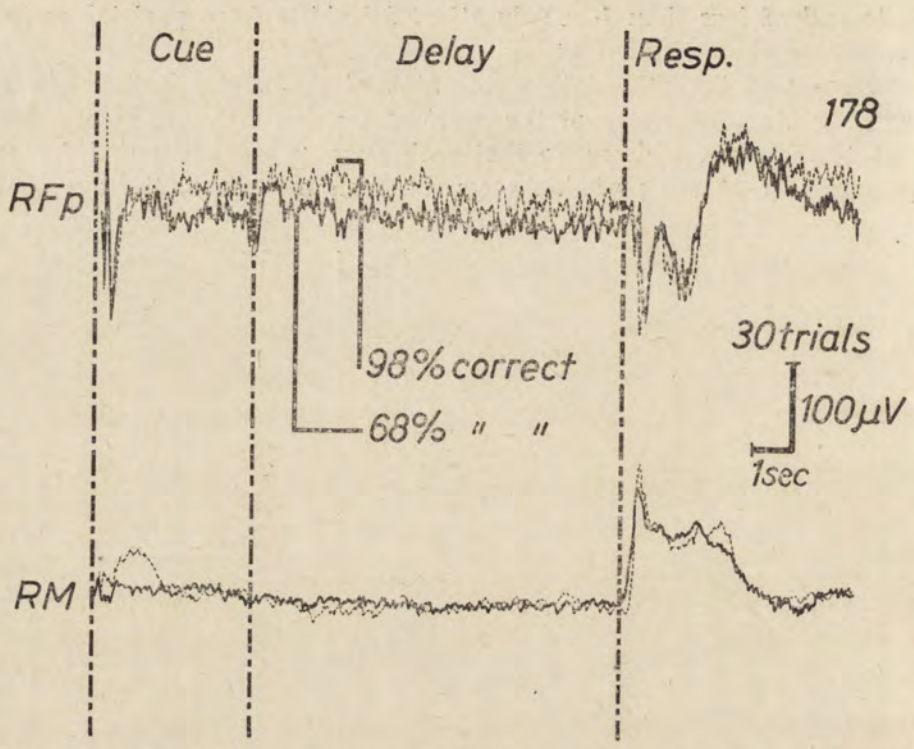

Fig. 7. Averaged ECG traces during correct and incorrect 8 sec. DR performance for monkey 178. Averages are for 30 trials each with performance at 68% and 98% correct. For electrode locations see legend Fig. 6

of trials, but the magnitude of the prefrontal SP shifts was appreciably higher when the delay period was followed by the higher rates of correct responses. These results suggest that prefrontal shifts of greater magnitude are followed by higher rates of correct responses and support the hypothesis that negative cortical SP shifts reflect the state of excitation of the underlying cortical elements.

SP shifts with cues of differing durations: In order to evaluate whether the prefrontal SP shifts are functions of evoked potentials which are time-locked to the onset of the cue, the duration of cue presentations was increased by 2 sec steps in successive daily sessions, of 100 trials each. As seen by Fig. 8, the duration of the SP shifts increased as a function of the period of cue presentation, but always with a return to baseline during the early portion of the delay period. Of interest is the finding that with 8 sec cue presentation a second negative wave was seen which reached maximum negativity at the start of the delay period. Simultaneous recordings from occipital cortex revealed negative SP shifts

after the onset of the cue, followed by positivity and return to baseline at the offset of the cue.

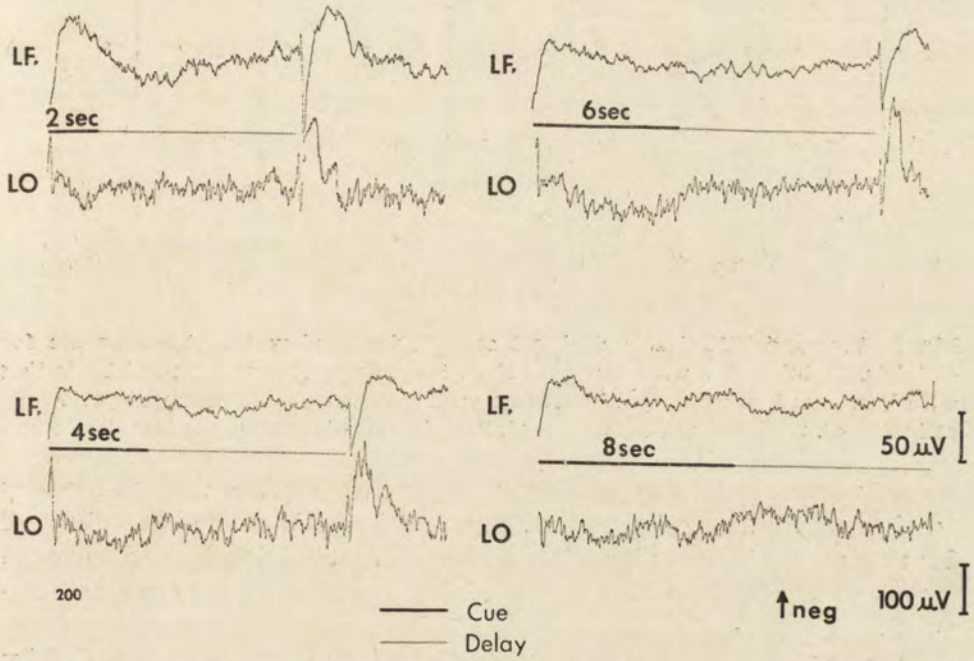

Fig. 8. Averaged ECG traces during 8 sec DR with cue presentation of 2, 4, 6 and 8 sec in right handed monkey 200. Averages are for 40 trials. For electrode locations see legend of Fig. 6

SP shifts during transfer of the responding hand: All monkeys had received extensive training with their preferred hands and the prefrontal SP shifts which have been described were most pronounced in cortex contralateral to this hand (Fig. 9, left column). When monkeys were then tested during one session of 100 trials with the previously restrained hand, marked increases were found in the magnitudes of SP shifts from *both* prefrontal cortices. By contrast, the SP shifts from premotor cortex were most pronounced in the hemisphere contralateral to the responding hand and decreased in the ipsilateral hemisphere. When on the following day monkeys were again tested with the preferred hand, the SP shifts from premotor cortices returned to the patterns obtained before the transfer of training, but the magnitudes of negative prefrontal shifts, remained higher than they had been before the transfer tests (Fig. 9). During continued training with the preferred hand the prefrontal shifts returned to the stable levels which were found prior to the intermanual transfer procedures. The scores of correct responses remained above 90% during

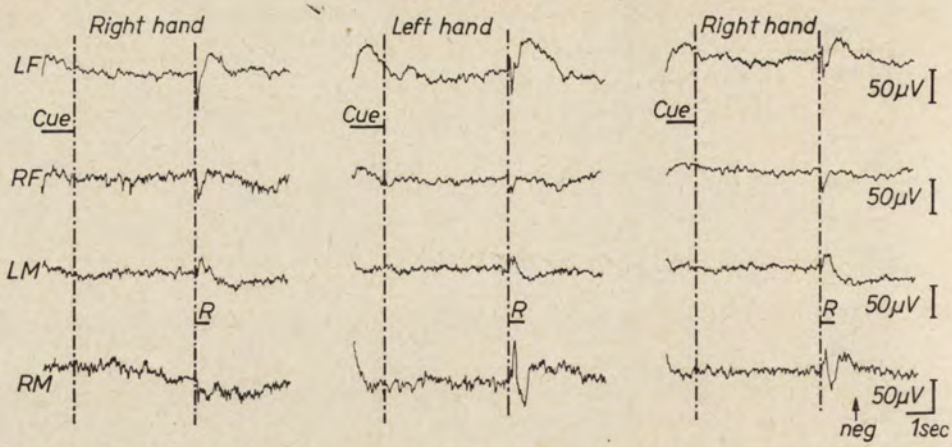

Fig. 9. Averaged ECG traces during 8 sec DR for monkey 200. Averages are for 40 trials. Training was with preferred right hand (left column), followed by testing with left, and then with right hand. Cue presentation and reinforcement period (R) as indicated. Surface negativity upward. For electrode locations, see legend of Fig. 6

these testing sessions, regardless of responding hand. When one monkey received continued testing with its non-preferred hand the magnitude of SP shifts from the now ipsilateral prefrontal cortex decreased during the course of training, whereas that from contralateral cortex remained elevated.

For two monkeys the averaged data of SP shifts were quantified by obtaining integrated planimetric measures with reference to 4 sec baselines during the final delay interval. The mean magnitudes of the SP shifts, expressed in microvolt-seconds, are presented in Table I. These

Table I

Effect of transfer of responding hand on magnitude of SP shift during Delayed Response performance

Electrode placement	SP shift[a] (microvolt-sec) with responding hand					
	monkey 200			monkey 203		
	right	left	right	right	left	right
L Principalis	47.18	50.00	30.79	8.43	11.86	9.40
R Principalis	11.86	14.24	18.40	16.81	22.42	20.16
L Premotor	1.19	0.95	1.66	113.95	27.99	62.98
R Premotor	0.00	37.85	10.83	6.23	39.07	6.61

[a] Mean response for 40 trials each.

results indicate that both contralateral and ipsilateral prefrontal shifts increase in magnitude during transfer from the right (preferred) to the left (non-preferred) hand, and that the magnitude of the shifts tends to decrease again during the second transfer to the preferred hand. By con-

trast, the magnitude of SP shifts in motor cortex is dependent on the hand that is used, with intermanual transfer resulting in increased SP shifts in cortex contralateral to the responding hand.

DISCUSSION

The recordings of electrocortical potentials during performance on the DR task indicate reliable surface negative SP shifts from each of several cortical areas. The shifts from each of these areas are related to specific components of the DR task, with occipital shifts reflecting the presentation of the visual cue and reinforcement lights, negative waves from premotor cortex occurring during movements of the contralateral arm, and SP shifts from prefrontal cortex reaching maximum negativity at the beginning of the delay period. Since surface negative SP shifts are interpreted as expressions of increased cortical excitation (O'Leary and Goldring 1964, Rosen and Stamm 1966), the present findings would indicate increased localized excitation of prefrontal cortex at the beginning of the delay period.

With regard to the specific implication of prefrontal cortex in the DR task, consistent results were obtained with both the technique of electrical stimulation and that of recording electrocortical potentials. Cortex in the banks of principal sulcus appears to be essential to correct DR performance during a relatively brief period just prior to and after the start of the delay. During the subsequent portion of the delay this cortical segment seems to become less important in mediation of the task, since the negative SP wave returns to baseline level and electrical stimulation during this period results only in minimally impaired performance. Moreoever, the involvement of prefrontal cortex in the DR task does not seem related to the onset or the duration of cue presentation, since we found that with cues of 2 to 8 sec duration, the maximal surface negativity and maximal disruption of correct performance with electrical stimulation were temporally linked to the start of the delay, but not to the onset of the cue.

The electrographic data revealed a second prefrontal surface negative SP shifts of considerable magnitude after completion of the instrumental response, i.e., during delivery of the reinforcement. This finding may be related to SP shifts which have been found associated with consummatory behavior by cats (Rowland and Goldstone 1963). These authors consider such shifts as reflecting generalized processes of orienting or arousal. An alternative explanation for these SP shifts is that they reflect a relatively non-specific neuronal feed-back system, rather than being related to consummatory behavior per se. This interpretation is supported by the findings that such SP shifts occur primarily in principalis cortex

contralateral to the responding hand and, furthermore, by the impaired DR performace with electrical stimulation during the reinforcement period (Stamm 1969). It seems highly unlikely that electrical stimulation which presumably disrupts these SP shifts would affect DR performance during subsequent trials, if the shifts merely reflected orienting or arousal responses. The impaired DR performance was obtained only with stimulation applied across the posterior segment of sulcus principalis, but not when the middle principalis region was stimulated. These results suggest the possibility of further differentiation of functional involvement by these small segments of prefrontal cortex.

The present findings have also revealed hemispheric differences in neuronal processes during DR performance. The prefrontal cortex contralateral to the trained (preferred) hand was consistently the source of the greater SP shift and also the site where electrical stimulation was most effective in disrupting correct DR performance. During transfer to the non-preferred hand the same cortical area yielded even greater surface negative shifts and also remained the principal site for impaired performance with stimulation. Stimulation of cortex contralateral to the non-preferred hand did not appreciably disrupt correct responses. These corroborative findings point to new approaches in the investigation of interhemispheric differences and cerebral dominance.

Our interpretation of surface negative SP shifts as reliable expressions of cortical excitation is further strengthened by the finding that the magnitude of the prefrontal shift was found greater during high levels of correct DR performance, than when lower rates of correct responses were obtained. During both of these testing periods no noticeable differences were found in the averaged SP shifts from premotor cortex.

We have found the techniques of localized electrical stimulation and of recording SP shifts to be productive approaches to our understanding of the neuronal processes and the functional role of prefrontal cortex. The cortical segment of principal sulcus in one hemisphere appears to be crucially implicated in the DR task *only* during the brief period before and after the start, but not during the subsequent longer portion, of the delay interval. In accordance with Konorski's (1967) conception of this cortical area as the locus of gnostic fields required for programming of complex patterns of spatio-kinetic acts, we may further specify the cortical limits and the critical period when this programming function occurs. The present techniques may also lend themselves to investigations of the dynamic neuronal processes which are involved in the establishment of such gnostic fields during the course of acquisition of new tasks and in relation to behavioral processes such as intermanual transfer and generalizations among related tasks.

This research was conducted with financial support by Grants GB-5256 and GB-6911 from the National Science Foundation. The authors express their appreciation to Howard Teich and George Sintchak for their technical assistance.

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Acta Biol. Exp. 1969, 29: 401—414

Lecture delivered at the scientific session held in commemoration of the 50th anniversary of the Nencki Institute

December 1968

A PROPOSED MECHANISM FOR DELAYED RESPONSE IMPAIRMENT IN PREFRONTAL ANIMALS

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If in a dog we make a prefrontal lesion limited to the region of the gyrus proreus, we will find that removal of this area neither increases locomotor activity of the animal, nor affects performance of a Pavlovian differentiation task in which one stimulus is reinforced by food, and another is not. If however, the animal has been trained before, either on a delayed response or a delayed alternation task, we will certainly find that this lesion produces a severe deficit on these two tests.

What are the common factors present in these two tasks that provoke difficulty in prefrontal animals' performance?

In the delayed response task the dogs are trained in a big room with three foodwells. A buzzer is mounted on the top of every foodwell. At the end of the intertrial interval, before each trial starts, the animal is leashed at the starting platform. Then a buzzer is sounding for 3 sec on one of the foodwells, determining the correct foodwell for a given trial. After certain period of delay, usually of 1 min, the animal is unleashed and allowed to make his choice. If the animal chooses the correct foodwell, that is, that signalled by the buzzer, the response is followed by delivery of food at that foodwell. If, after being released, the animal approaches the wrong food container, the response is not reinforced by food.

In the delayed alternation task the animals are trained in the same experimental room with only two foodwells available. There is no special presentation of an exteroceptive stimulus determining the correct

foodwell for a given trial — the animal's response, except for the preliminary trial, is determined by the preceding trial. The animal solves the task, if he alternates between the two side foodwells on successive trials.

In the intertrial intervals the animal, as on the delayed response test, may be leashed at the starting platform — in which case the unleashing evokes the animal's response towards the foodwells. He may be also tested under different conditions and remain free in the intertrial intervals if trained to respond to an auditory stimulus — in which case each presentation of the tone evokes the response of approaching a foodwell.

What are the common elements of the delayed response and delayed alternation task?

Both involve more than one, usually three (on the delayed response task), or two (on the delayed alternation) instrumental locomotory responses reinforced by food. The stimulus determining which response is correct on a given trial is not present at the moment of responding. The animal responds after a delay, and the response is performed to the actual releasing stimulus (either unleashing or a tone), which is the same on each trial. The role of the releasing stimulus is to *evoke* the response that had been *determined* by the predelay cue (Konorski and Ławicka 1959).

Since in both tasks more than one instrumental response leads to food reinforcement, it might be assumed that in order to respond with the correct movement, the animal must be able to suppress the tendency to respond to the other foodwell (or foodwells) on that trial. This suppression, called act-inhibition by Stanley and Jaynes (1949), was suggested by these authors as a hypothesis explaining the phenomenon of the delayed response impairment discovered first by Jacobsen (1936) in the effect of frontal lobectomy in the monkey.

Several years ago in a series of studies carried out in our laboratory (Konorski et al. 1952, Brutkowski et al. 1956, Ławicka 1957a, Brutkowski 1959) it was found that prefrontal lobectomy in dogs produced a severe impairment on the Pavlovian go-no go differentiation task, which was manifested as a difficulty in suppressing responses on negative trials and in the intertrial intervals. Additionally, it was shown that the same animals also exhibited a severe deficit on the delayed response task (Ławicka 1957b, Ławicka and Konorski 1959) thus extending Jacobsen's finding to this species.

Since these two symptoms were related to prefrontal lobectomy, it seemed not unreasonable to suppose that they may derive from a single deficit, manifested on the first task as a difficulty in refraining from responding to the negative stimulus, and on the second as a lack of capability to suppress the non-correct responses on successive trials. On

the other hand, it could also be assumed that these two deficits are separable and may be dissociated in the effect of partial lesions within the dog's prefrontal area (Ławicka 1957b, Ławicka and Konorski 1959). To test the latter hypothesis we began to look for a partial lesion leading to the selective delayed response impairment.

In the meantime, observation of the animals' behavior after prefrontal lobectomy in the delayed response task revealed that the animals gradually improve in the course of postoperative retraining: this was mainly due to the fact that they learnt to preserve their bodily orientation towards the foodwell, signalled by a determining stimulus at the beginning of each trial. Whenever they changed their orientation during the delay period, which as a rule happened on the trials with intradelay distractions, they responded at a chance level. This led us to the conclusion that the deficit we observed in these animals may be attributed to a loss of immediate memory of directional cues. Thus, we accepted Jacobsen's (1936) original notion limiting it to the directional cues. Furthermore, since the prefrontal area is situated rostrally to the so-called premotor area (Woolsey et al. 1952), which, if stimulated, gives rise to the head, trunk and eye movements, we regarded the prefrontal cortex as its adjacent association area (Ławicka and Konorski 1963).

However, this interpretation of prefrontal animals' delayed response deficit in terms of recent memory loss had to be rejected on the basis of further experiments performed on cats (Ławicka and Konorski 1961). In this study, prefrontal cats were found considerably deficient on the delayed response test, in which they made two kinds of perseverative errors: either "last response" errors, when they repeated the last reinforced response from the preceding trial, or "single response" errors, consisting of always approaching the same foodwell in many successive trials. However, what was unexpected was the finding that in spite of these error tendencies, the animals often after making an error, instead of coming back to the starting platform, attempted to correct themselves by approaching the correct foodwell (Fig. 1). These corrections runs were never reinforced (since as a necessary condition for food reinforcement the animals were required to approach directly the signalled foodwell), and, as may be seen in Fig. 2 they may become extinguished in the course of testing, presumably due to their nonreinforcement procedure. (It should be recalled that the animals were tested in a triple choice situation which still enabled scoring of corrections under the double choice conditions.)

The existence of "correct" corrections in cats after an error has been made provided a strong argument against the interpretation of frontal impairment as arising from a loss of the recent memory of directional

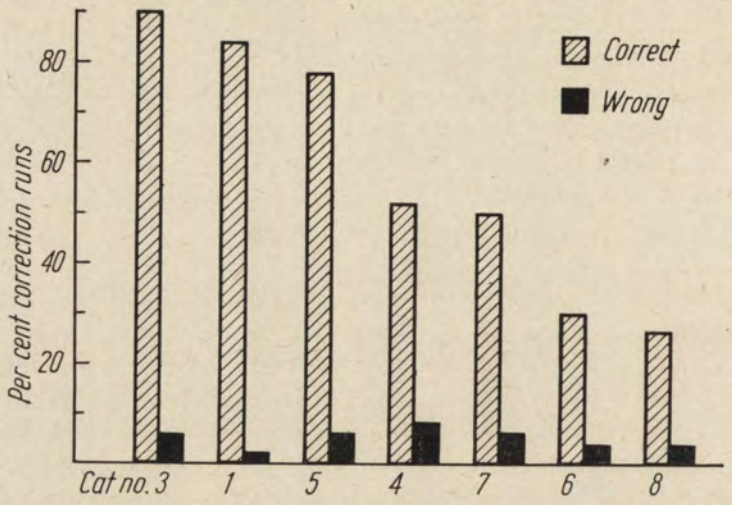

Fig. 1. The percentage of errors with corrections in prefrontal cats. Each hatched bar denotes the percentage of errors with "correct" corrections, each black column — percentage of errors with wrong corrections

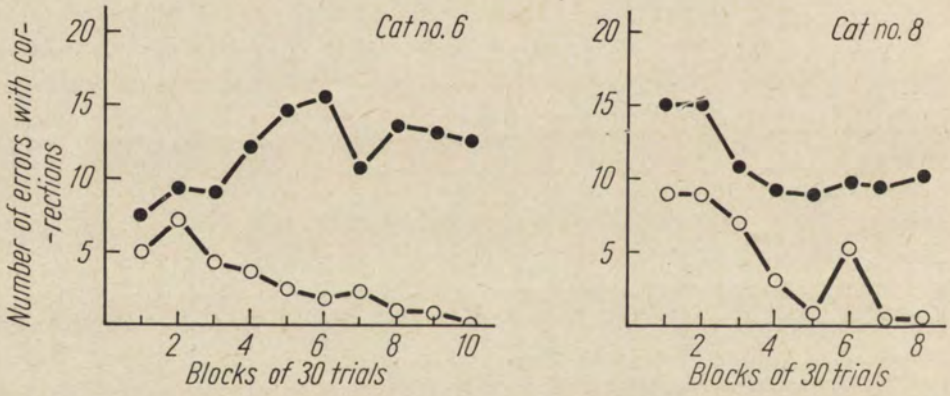

Fig. 2. The number of errors and their corrections. Each block represents 30 delayed response trials. Black circles — errors, white circles — corrections

cues; moreover, the result of a partial lesion experiment performed on dogs has demonstrated (Ławicka, in preparation) that these animals, too, attempted to make corrections after making an error, although, as may be seen in Fig. 3 their tendency to correct themselves was never so high as that observed in cats, presumably because of their faster extinction.

The results of the experiment on dogs (Ławicka et al. 1966) in which, according to Kreiner's myeloarchitectonic map (Kreiner 1961) the comparison between the three types of prefrontal lesions — presylvian, orbital

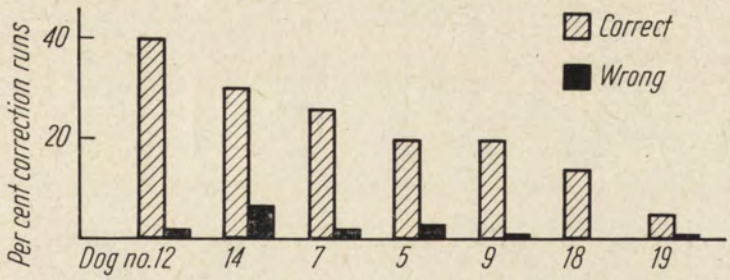

Fig. 3. The percentage of errors with corrections in prefrontal dogs. Explanation as in Fig. 1

and proreal — was made (Fig. 4, 5), indicated that the proreal lesion was critical for the delayed response impairment. The proreal animals showed a severe and longlasting impairment on that task (Fig. 6), especially if compared with the preoperative learning when almost all animals reached criterion immediately.

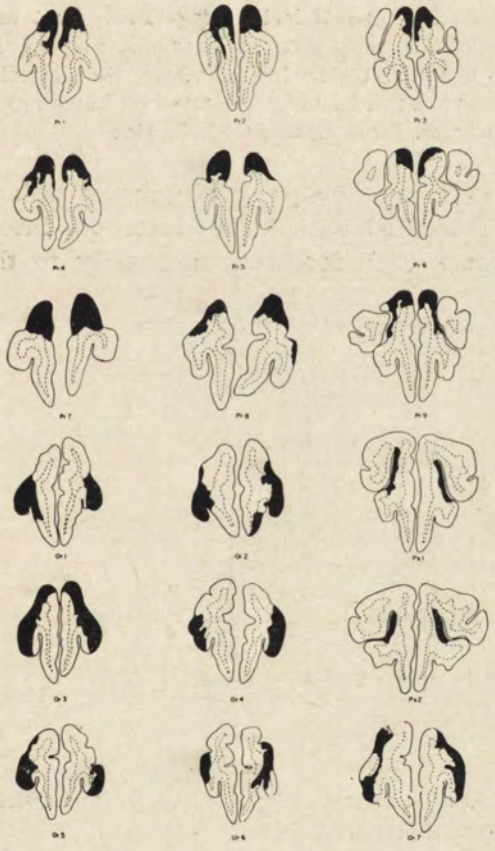

Fig. 4. Cross-sections through each animal's lesion, indicated in black. To facilitate comparison among animals and groups, rostrally located sections have been placed to the left, caudally located sections to the right. Pr = proreal; Or = orbital; Ps = presylvian. From Ławicka et al. 1966

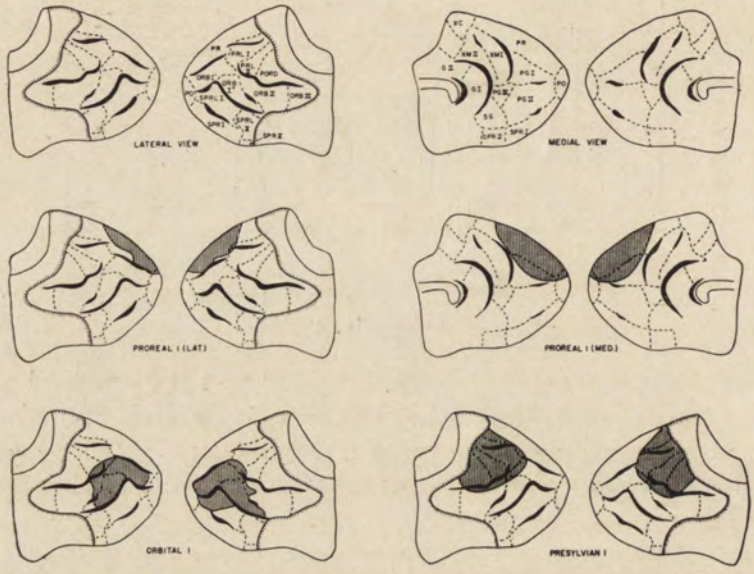

Fig. 5. Representative reconstructions of each type of lesion (dogs Pr 1, Or 1 and Ps 1), transferred to standard diagrams of Kreiner's myeloarchitectonic map of the prefrontal region. Lesions indicated by shading. In the lateral views, the posterior bank of the presylvian sulcus has been removed at its base (indicated by hatching) in order to expose the anterior bank. From Ławicka et al., 1966

A severe deficit was found also in another group of animals trained on the delayed alternation task presented with 1-min intertrial intervals. The animals learnt to approach each foodwell alternately to the

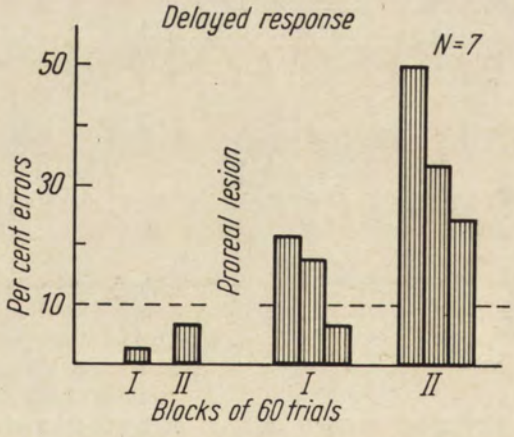

Fig. 6. Average performance of the proreal group on the two delayed response problems; I = 60 sec delay; II = 60 sec delay with intradelay feeding. From Ławicka et. al. 1966, modified

onset of a tone evoking a response in successive trials. In the effect of the proreal damage the dogs required a much larger number of errors to reattain criterion than they had required preoperatively (Fig. 7).

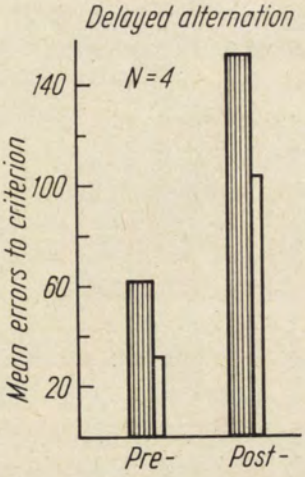

Fig. 7. Mean errors preceding criterion on delayed alternation. White bars — repetitive errors

Thus, the cortical prefrontal area focally concerned with the delayed response type of problem appeared to be proreal area. Moreover, this area was found to be selectively involved in that function, since proreal removal produced no deficit on the Pavlovian go-no go differentiation task (Fig. 8). On this task the animals were required to approach a food-

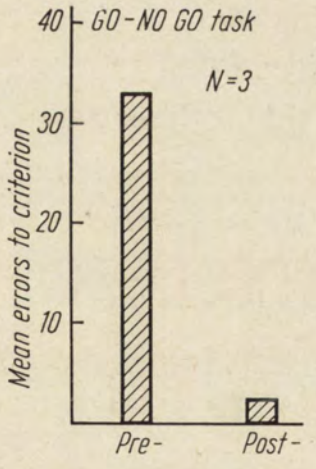

Fig. 8. Mean errors preceding criterion on the Pavlovian go--no go differentiation task

well to the positive tone only and to remain on the starting platform during the presentation of a negative tone, which was never followed by a food reinforcement. The possibility that the proreal region is not cru-

cially involved in the go-no go differentiation problem is also supported by the other studies (Szwejkowska et al. 1963, Brutkowski and Dąbrowska 1966) in which placing the forefoot on the feeder was used as a positive instrumental response reinforced by food.

On the basis of the above differential effects produced by partial prefrontal lesions on a series of tests, the possibility of dissociation of the two frontal deficits, one observed on the delayed response and another on the go-no go task, has been confirmed indicating, that the prefrontal ablation producing the delayed response deficit does not interfere with performance of the Pavlovian differentiation task (cf. Brutkowski et al. 1960, 1963). What remained unclear, however, was the nature of the proreal impairment. Inferring from the fact that the animals' deficit was selectively related to the tests involving the discrimination within at least *two* positive instrumental responses, but leaving the test with a single positive response, involved in Pavlovian differentiation, unaffected, it might be suggested that the animals fail in these two tasks because of perseverative interference; or, in other words, their failure may be attributed to the inability to shift from one form of positive response to another (Settlage et al. 1948, Stanley and Jaynes 1949, Settlage et al. 1956, Ettlinger and Wegener 1958, Brush et al. 1961, Ławicka and Konorski 1963).

To test this hypothesis the animals were trained on a task in which two tones were presented from a single loudspeaker, one tone signalling the response to the left, and another to the right foodwell, with no intervening delay between the stimulus and response; the trials were se-

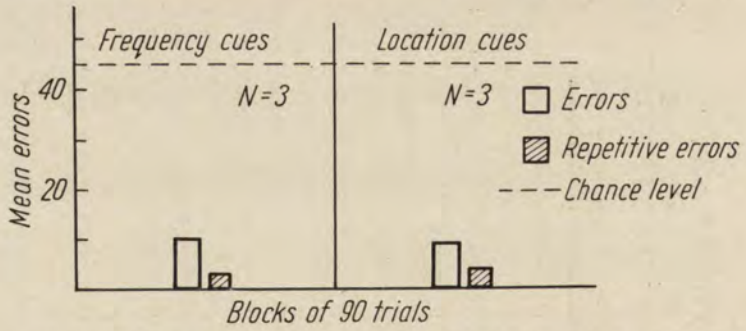

Fig. 9. Mean errors on the first postoperative block of 90 trials (5 successive experimental sessions)

parated by 1 min intertrial intervals. Although the task was very difficult for normal dogs (Ławicka 1964, 1969), nevertheless, the proreal animals appeared to be completely undisturbed by the proreal damage (Fig. 9, frequency cues). This result provided a strong argument against

perseverative interference, and additionally, argued against any discriminatory deficit related to the directional responses.

The finding was still not conclusive with regard to the directional cues involved in both delay test; these cues may have been critical for the disrupted animals' performance. Therefore, in the second series of experiments another group of dogs was trained with the auditory location cues in which the same tone was presented from two loudspeakers differently located at the starting platform, one cue signalling the response to the left, and another to the right foodwell. When tested for retention after the proreal damage, no evidence of impairment has been found also in this group (Fig. 9, location cues).

The last experiments indicating that the proreal animals are unimpaired on the go left-go right task with no intervening delay, raised the question of whether the delayed response impairment may be specifically related to the factor of delay. One possible interpretation of this deficit attributing it to a loss of the short-term memory of the determining cue, could be rejected on the basis of experimental evidence that the prefrontal animals after making an error were able to approach the correct foodwell. Another interpretation of the animals' deficit was related to the functional role of the releasing stimulus.

It may be recalled that on the delay tests the animals response is preceded by the determining cue and actually occurs to the releasing stimulus. Thus the releasing stimulus, directly preceding different instrumental responses, according to the basic law of instrumental conditioning has a chance to become associated with each response performed and reinforced immediately after it. As a result, the same stimulus being followed by more than one instrumental act can not acquire an adequate, signalling role ensuring the correct performance. This consideration pointed toward the releasing stimulus as a possible source of interference in the animals' performance.

In an attempt to test its role in the delayed response situation, the testing procedure on that task has been changed by introducing "sham" trials. A "sham" trial differred from a normal one in that no determining stimulus was presented: the animal was leashed at the starting platform, waiting there for 1 min, and then released. If, after being released, he approached a foodwell, no food was presented. Under the new condition of testing every normal trial was followed by a series of "sham" trials till the animal, after being released, remained at the starting platform (Table I). In other words, following every normal trial the releasing stimulus was submitted to acute extinction and only after that, the next normal trial was given.

Table I

An example of the "sham" trials procedure. Each normal trial is followed by a series of "sham" trials until the animal remains at the starting platform
(Dog No. 15, January 16, 1963)

No. of normal trial	Time in min	Determining stimulus	Delay in min	Response[a]	Food reinforcement[b]
1	1	$Buzzer_1$	1	R_1	+
	3	—	1	R_2	—
	5	—	1	R_3	—
	7	—	1	R_1	—
	9	—	1	R_1	—
	11	—	1	R_3	—
	13	—	1	R_2	—
	15	—	1	R_1	—
	17	—	1	R_2	—
	19	—	1	R_3	—
	21	—	1	R_1	—
	23	—	1	R_3	—
	25	—	1	no resp.	—
2	27	$Buzzer_2$	1	R_2	+
	29	—	1	R_2	—
	31	—	1	R_2	—
	33	—	1	no resp.	—
3	35	$Buzzer_1$	1	R_1	+
	37	—	1	R_3	—
	39	—	1	no resp.	—

[a] R_1, R_2, R_3, denote responses towards respective foodwells.
[b] + food presented, — no food presented.

The new testing procedure revealed that in prefrontal animals the releasing stimulus has a strong tendency to elicit the approach responses to the foodwells in many successive "sham" trials (Ławicka and Konorski 1963, Konorski and Ławicka 1964, Ławicka, in preparation). Then, it appeared that if a normal trial is given following a series of "sham" trials, that is, after the acute extinction of the approach response elicited by the releasing stimulus, then the operated animals showed no impairment on normal delayed response trials. Thus, according to what has been discussed above, this finding supported the prediction that the releasing stimulus may acquire an interfering role in frontal animals' performance.

Although under these conditions of testing the deficit was observed no more in frontal Ss on the normal delayed response trials, the degree of these animals' disturbance was reflected in the total number of "sham" trials required by each animal for extinction of the releasing stimulus. As may be seen in Fig. 10 there exists a positive correlation between the number of errors each animal made on the last series of trials directly

preceding the introduction of the "sham" trials procedure, and the number of "sham" trials required for extinction of the releasing stimulus (Spearman rank correlation coefficient r_s 0.92, p. < 0.01, Siegel 1956).

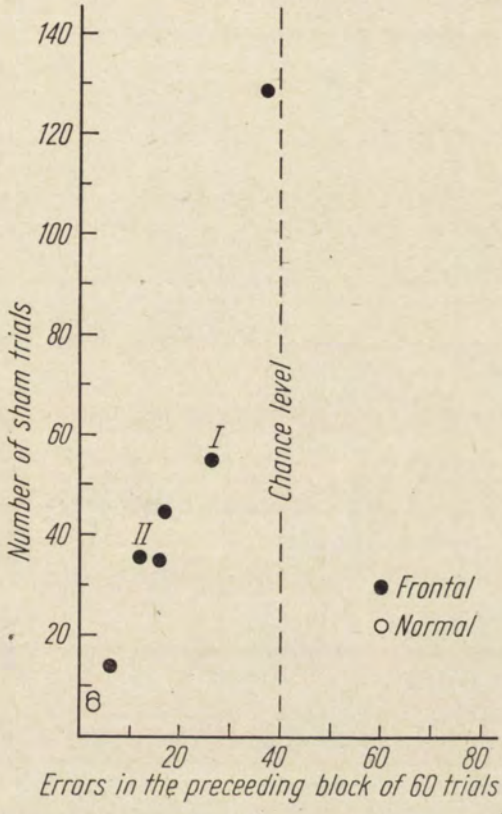

Fig. 10. The number of "sham" trials required by individual Ss per 15 normal delayed response trials. Abscissa, number of errors each S made in the block of 60 trials directly before the introduction of the "sham" trials procedure. Different animals are submitted to the "sham" trials at different stage of their postoperative training. I, II; the same dog tested in the early (I) and later (II) postoperative period

Since the stronger the conditioned stimulus, the larger the number of trials necessary for its extinction, this result may be interpreted as an evidence that the strength of the releasing stimulus in prefrontal Ss in the delayed response situation is positively correlated with these animals' deficit on that task.

One possible objection against this interpretation of results obtained in the series with "sham" trials might be the fact that due to this procedure the usual, 1 min intertrial intervals, between the normal delayed

response trials has been considerably prolonged. However, the 1 min intertrial intervals do not seem to be the critical variable since each animal's impairment was also reflected on the *first* trial of postoperative experimental sessions (cf. Wilson et al. 1963). Also, it should be added, that 1 min intertrial intervals did not prevent the proreal dogs from the correct choice-response on the go left-go right task.

If the prefrontal animals' impairment on the delayed response task may be related to the interfering role of the releasing stimulus, then the same factor might provide a satisfactory explanation to account for the deficit observed on the delayed alternation task.

In conclusion, we should consider the intriguing question why does the releasing stimulus in these two tasks increase its strength in the operated frontal animals. One possibility would suggest that this stimulus, in the effect of prefrontal ablation, starts to evoke an increased orienting response and, in consequence, forms strong association with each response performed and reinforced immediately after it, overshadowing the trace conditioned reflex based on the determining cue and thus resulting in errors.

Do we have any other experimental evidence that would suggest that the prefrontal animals show an increased response to the actual external stimuli, or changes in the habituation processes. If we take into consideration other experimental procedures and experiments performed on other animals, we can easily notice that a number of authors drew attention to the fact that the prefrontal animals become hyperreactive (cf. Rosvold and Mishkin 1961) if submitted to external stimulation (French and Harlow 1955, Isaac and DeVito 1958, Gross 1963). Moreover, there exists also a good experimental evidence indicating that habituation of various types of orienting reactions is strongly impaired after the prefrontal lesions (Glaser and Griffin 1962, Griffin and Pearson 1967, Griffin and Pearson 1968, Dreher and Żernicki 1969). It is very tempting to think that all these facts may depend on a similar or even identical mechanisms as those described in the present paper.

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ANNOUNCEMENTS

The International Society for the History of the Behavioral and Social Sciences (ISHOBSS) will meet May 8, 9, 10, 1970 at the University of Akron, Akron, Ohio.

The University of Akron is the site of The Archives of the History of American Psychology. The meetings will take advantage of this and there will be a number of exhibits and programs which will draw on the resources of the Archives.

Registration forms and room applications may be obtained immediately.

Submitted papers and proposed symposia should be received by February 1 for presentation to the members of the program committee. Notice of the content of the program will be made by March 15.

All inquiries concerning the program should be addressed to:

Dr. John A. Popplestone
Department of Psychology
The University of Akron
Akron, Ohio 44304

From August 10 to 16, 1970, in Braşov (Romania) the Regional Congress of Physiological Sciences will be organized under the sponsorship of the International Union of Physiological Sciences (IUPS). Any information concerning participation may be obtained from the: Romanian National Organizing Committee, Institute of Physiology, Bd. 1 Mai No. 11, Bucharest VIII, Romania.

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PUBLIKACJI ACTA BIOLOGIAE EXPERIMENTALIS

Zamówienia i przedpłaty na publikację przyjmują: od instytucji i wszelkiego rodzaju zakładów pracy Oddziały i Delegatury „Ruchu"; od prenumeratorów indywidualnych: Centrala Kolportażu Prasy i Wydawnictw „Ruch", Warszawa, ul. Wronia 23, konto PKO Nr 1-6-100020.

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PAŃSTWOWE WYDAWNICTWO NAUKOWE
WARSZAWA 1969

Printed in Poland

Cena zł 42.—

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