Electrical activity of the brain: Mechanisms and interpretation

S. M. Osovets, D. A. Ginzburg, V. S. Gurfinkel', L. P. Zenkov, L. P. Latash, V. B. Malkin, P. V. Mel'nichuk, and E. B. Pasternak

I. V. Kurchatov Institute of Atomic Energy, Moscow,
M. F. Vladimirskiĭ Moscow Regional Clinical Institute,
Institute of Problems in Data Transmission, Academy of Sciences of the USSR,
I. M. Sechenov First Moscow Medical Institute,
Scientific Research Institute for Biological Testing of Chemical Compounds,
and A. M. Gorkiĭ Institute for World Literature, Academy of Sciences of the USSR
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Physical analogies are used to develop ideas on the origin of spontaneous oscillations in the electrical activity of the human brain and on the variation in these oscillations that accompany changes of state and of type of activity. A possible functional role of such oscillations in the overall activity of the brain and mechanisms responsible for certain pathologies of brain activity are examined. Existing phenomenology and current hypotheses are used as a basis for suggesting that: 1) spontaneous rhythms on the electroencephalogram (EEG) are due to the interaction between a finite number of autogenerators (pacemakers) formed by the neuronal populations of thalamic nuclei and functional units in the cortex that exhibit the properites of a passive oscillatory loop; 2) because of its well-defined nonlinearity, the interaction between thalamic autogenerators of different natural frequency leads to the generation of a great variety of observed EEG patterns that accompany different types of brain activity (including responses to external disturbances), all of which is a consequence of recent advances in the theory of nonlinear oscillations that have led to the discovery of "strange attractors"; 3) the subdivision in the brain of the pulsed flow of information into "specific" and "nonspecific", where the latter has a modifying influence on interactions between thalamic pacemakers and on the appearance of special multiperiodic patterns that are characteristic for different events, leads to a distributed fixation of long-term memory traces when the nonspecific and specific flows converge on a neuron memory substrate, and these traces can be read by a single characteristic multiperiodic pattern; and 4) the mechanism responsible for the appearance of paroxysmal discharges in certain specific types of epilepsy and the associated characteristic EEG phenomena (including frequency division) ensues from pathologically modified interaction between thalamic pacemakers and functional units in the cortex, which exhibits resonance properties.

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CONTENTS

INTRODUCTION

Dynamic analogies and the corresponding modeling have resulted in a better understanding of the mechanisms underlying a great variety of phenomena, not only in physics, but also in natural and social sciences that are quite remote from physics. Until recently, this approach was restricted to the study of transient regimes, equilibrium states, and oscillatory processes that converged to simple or complex limit cycles. This approach, however, is known to be quite inadequate for the analysis of many important phenomena. The discovery of Landau-Hopf-type bifurcations and, subsequently, of the so-called strange attractors, i.e., regimes in which a dynamic system becomes a generator of multiperiodic and random signals,[1-5] have substantially enriched the theory of nonlinear oscillations and have resulted in an expansion of the range of phenomena that can be examined on the basis of analogies. This applies, in particular, to periodic processes studied in biology.

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Among the more important phenomena of this kind, we must include the electrical rhythms of the brain that are recorded from the skin of the head in the form of relatively slow oscillations in the electrical potential, known as the electroencephalogram (EEG). In this paper, we attempt to use the theory of nonlinear oscillations to develop an explanation of the structure of the EEG and of the mechanism responsible for it, and to present certain ideas on the functional significance of brain rhythms. This attempt is topical because, despite substantial advances in the practical exploitation of EEG phenomenology (in physiological studies, medicine, and psychology), and despite the fact that it is now a century-and-a-half since the discovery of the phenomenon, the theory of the origin of the electrical rhythms in the brain and, especially, of their role in brain activity insofar as it affects the psyche and behavior, has not emerged in any kind of final form. The reason for this can be traced to the unusual complexity, whereby the brain elements, ganglia, and blocks are organized to produce integrated action.

The absence of such a theory has meant that diametrically opposite views are being held about the functional role of the electrical rhythms in the brain. These range from the acknowledgment that they are exceedingly important and, possibly, determine the very basic aspects of the integrated activity of the brain, to the belief that these rhythms are mere noise which, at best, can serve as a crude indicator of the operation of individual brain blocks, but carry no independent functional load.

We must not conclude that this situation has arisen as a result of a lack of attention to the problem. On the contrary, an enormous amount of work has indeed been done, and various experiments with animals and humans have been carried out in parallel with attempts to construct models and circuits consisting of neuron-like elements with excitatory and inhibitory couplings. These circuits are looked upon as a kind of abstract primary net, and are subjected to theoretical analysis with a view to identifying characteristic features in their behavior and, in particular, their oscillatory properties. These studies have been carried out both analytically and by computer simulation. Some of these circuits can probably be regarded as certain analogs of devices reproducing the operation of real objects, i. e., the brain rhythm generators. However, this somewhat abstract approach to brain processes, which ignores the subdivision of the brain into different structures with the associated specific organization of neuronal nets and the actual properties of the interaction between them, has had an important effect on the significance of the results obtained. At best, the results of this analysis indicate a possible approach to the solution of problems in terms of a certain number of equivalent circuits, but provide no answer to the basic questions, namely, how does the brain actually solve a problem, how is this method of solution inscribed in the actual structural organization of the brain, and what are the basic interactions in the brain?

In this review, we take as our starting point the notion that the electrical activity of the brain is of great functional significance, and try to explain some of the working features of both healthy and diseased brain in terms of the interaction between oscillatory processes in specific structures, namely, the cerebral cortex and certain deeper formations such as, in the first instance, the thalami and the reticular formation of the brainstem.

The fact that we are publishing our review in this particular journal is due to a number of related circumstances. Since our review exploits approaches and analogies that are largely based on the physical theory of nonlinear wave processes, it would be interesting to have the response of physicists both to specific results of this approach and to the validity of its foundations. The authors hope that, by attracting the attention and interest of physicists to this particular range of problems, they will contribute to further advances in this field, especially since our presentation is an attempt to map out only major landmarks along a very tortuous path. At this particular stage, any help in developing the physical aspects of the problem would be particularly desirable and valuable although, of course, the final word would have to be left to the appropriately planned neurophysiological and psychological experiment.

The presentation and appreciation of the problems that we shall review give rise to a number of difficulties. Medicine and biology are firmly established experimental sciences with their own dictionary, range of concepts, and methodologies. We must therefore begin with an introductory account of the electroencephalogram, the structure of the brain, the functions of its main components, and the basic building block of the nervous system—the nerve cell (neuron) and its working. This introductory material will form the first section of our paper. Readers familiar with this material may begin with the second section.

1. ELEMENTS OF NEUROPHYSIOLOGY (CONCEPTS AND LANGUAGE)

a. Electrical brain waves—the electroencephalogram

Electroencephalography is the technique of recording and interpreting oscillations in the electrical potentials of the brain. Between 1928 and 1934, the Austrian psychiatrist, Hans Berger, published a number of fundamental papers in which he gave, for the first time, a systematic description of the electrical activity of the brain (the electroencephalogram—EEG) recorded with the aid of electronic amplifiers in different states, namely, wakefulness, natural sleep, anesthesia, and disturbed brain metabolism. The EEGs corresponding to these different states of the brain are found to be different and constitute complicated curves consisting of oscillations of different frequency and amplitude.[1)]

[1)] The magnetoencephalogram (MEG) was recorded in 1968. It involves measuring the magnetic field of the brain instead of the electrical potentials, i.e., in the final analysis, currents flowing between different portions of neurons. The magnetic field at 2 cm from the skull is 10^{-7}–10^{-8} Oe.

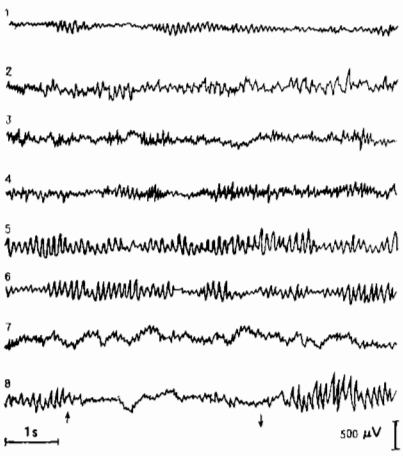

FIG. 1. Spontaneous EEG rhythms at different points in the cerebral hemispheres of the human brain (exposed during neurosurgery)[8]. Different frequency ranges can be seen. Recordings: 1—anterior frontal and 2—intermediate frontal cortex, 3 and 4—precentral and posterior central regions, 5—parietal and 6—posterior temporal regions, 7—hippocampal gyrus (part of the limbic system), 8—occipital part of the cortex. For explanation of terms see Section 1c, Figs. 5 and 6. Arrows at the bottom of the figure indicate opening and closing of eyes. Calibration: 1s, 500 μV.

Continuous rhythmic electrical activity is recorded[6,7] when suitable electrodes are attached to the scalp at the top of the cranium in a state of quiet wakefulness (psychological and physical relaxation, usually with eyes closed). Since this activity cannot be associated with a specific external disturbance, it is usually referred to as "spontaneous." In most people, the activity is dominated, especially at the back of the head (the parieto-occipital region) by the alpha rhythm with frequencies between 8 and 13 Hz. This takes the form of regularly propagating waves whose amplitude does not usually exceed 100 μV, and the waves themselves take the form of a sequence of rises and falls with periodically varying amplitude (Fig. 1). In addition to the alpha waves (Fig. 1, tracings 1, 5, 6, and 8; Fig. 2, tracing II), there are also more rapid oscillations, called the beta rhythm (14–22 Hz—the "low-frequency" rhythm, shown by tracings 1, 4, 7 of Fig. 1 and IV of Fig. 2, and above 22 Hz—the "high-frequency" rhythm, illustrated by tracings 3 and 4 of Fig. 1 and I of Fig. 2). There are also the slower theta rhythm (4–7 Hz, tracing 2 in Fig. 1) and the delta rhythm (0.5–3.5 Hz, tracings IV–VI in Fig. 2). The last two types of activity in healthy persons are poorly defined in the waking state but are the dominant pattern during sleep (Fig. 2). The beta rhythm is best defined in the anterocentral parts of the brain.

It is clear from Fig. 1 that the waves constituting the rhythm are not monochromatic. The frequency of the dominant rhythm fluctuates within a characteristic interval of 1 Hz or more. The waves are usually deformed as a result of the superposition of oscillations of different period, so that Fourier analysis of even outwardly homogeneous waves reveals the presence of a number of component frequencies.

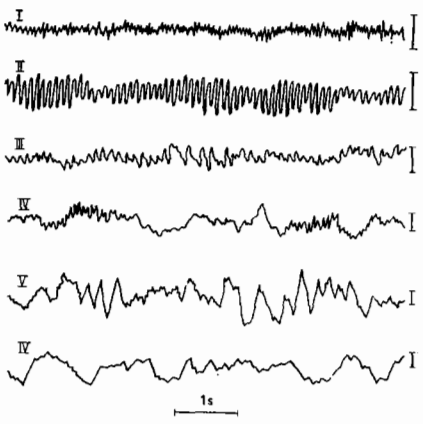

FIG. 2. Spontaneous EEG rhythms of healthy man in different states of wakefulness and sleep (recorded from the skin of the head[8]). I—active wakefulness, concentrated attention, II—quiet wakefulness, III–VI—"slow" sleep (respectively: stage 1—drowsiness, stage 2—"sleep spindles", stages 3 and 4—delta-sleep); type III EEG corresponds to "rapid" sleep with episodes of type I and II. Calibration: 1 s, 50 μV.

The power spectrum and the spatial and dynamic parameters of the EEG recorded for different persons exhibit well-defined individual features which appear to be genetically based, since practically identical EEGs have been recorded only for identical twins. The EEG pattern of a healthy individual remains relatively constant and verifiably so over many years.

Simultaneous recording of the EEG from the scalp and from exposed cortex has shown that all these rhythmic oscillations in the potential do, in fact, originate in the brain.[2)] It has thus become possible, for the first time, to examine the operation of the brain not only on the basis of indirect indicators, i.e., external effects such as behavior, verbal accounts of subjective experience, motor reactions, and vegetative reactions (secretion of iron, cardiovascular and other changes in the "internal housekeeping" of the organism), but also on the basis of direct indicators directly reflecting the operation of the brain substrate.

b. Connection between the EEG and brain functions

There were hopes, during the early stages, that the EEG would supply direct evidence for the basic features of the operation of the central nervous system (CNS) that were established by C. Sherrington in relation to congenital mechanisms, and by I. P. Pavlov in connection with acquired types of brain activity that were thought to be connected with psychological activity and the behavior of the higher animals and man. Nothing like it was actually detected. The EEG rhythms that are so well defined in the state of relative relaxation persist but become more dynamic and variable in the course of normal activity with eyes open. Unexpected signals, significant changes outside or inside (for ex-

[2)] Minor differences between frequency-amplitude characteristics are connected with the removal of the shunting action of skull tissue and brain fluid when the EEG is recorded from the exposed brain.

ample, as a result of the thought process and recall), emotional reactions, and learning usually provide an initial change in the EEG in the form of a reduction in the amplitude, a weakening or disappearance of the alpha rhythm. As soon as the learning process is over, the signals and functions resume their normal course and the original rhythm is re-established even though the particular individual remains engaged in his normal activity, which may well be highly intellectual.

Real life involves psychical activity with continuously varying impressions and a time-sequence of automatic or nonautomatic actions in the course of normal activities, which take the form not only of movements, but also conscious and subconscious intellectual processes, sensations, and perception of external signals. This is hardly a passive, mirroring process, and must be regarded as a particular activity of the brain in which it organizes the functions of sensory systems. The dynamic character of the EEG patterns within the limits of the above-mentioned relatively small range of variability in their characteristics, which involves a variation in the amplitudes, a shift in frequencies (which are smeared out within this range), a variation in phases, changes in the spindle pattern, and the onset of flat periods (with possible differences between different parts of the cerebral hemispheres), are all well defined and constitute one of the most striking features of the electrical rhythm of the brain in a wakeful state. This dynamic variability often cannot be traced at a particular time and interpreted in detail, so that continuous transient variations in the EEG rhythms (a kind of "microdynamics") are usually ignored in electroencephalographic practice and are covered by general estimates of the "background" over a relatively long period of time. As indicated above, such estimates are quite homogeneous and static.

Relatively ordered, regular variations in the EEG rhythms are found during sleep[9] and take the form of a cyclic repetition of four or five patterns. To a considerable extent, this has been the basis for the identification of alternating phases and stages of sleep (tracings III–VI in Fig. 2). Normal sleep begins with the initial cessation of the alpha rhythm and the appearance of small-amplitude activity with groups of theta and beta waves (stage 1, drowsiness; tracing III in Fig. 2). This is followed by the appearance of spindles associated with the 14–16 Hz beta rhythm (stage 2, "sleep spindles", tracing IV in Fig. 2), which are eventually replaced by delta waves, whose amplitude and number gradually increase, whilst the frequency falls from 2–3 to 0.5–2 Hz (stages 3 and 4, the so-called "delta sleep", tracing V in Fig. 2).

Next, after a short period of activity corresponding to stage 2, the EEG again becomes more quiescent, with frequency brief episodes of theta or even alpha rhythm, accompanied by the relaxation of tonic tension in neck muscles and rapid eye movement. This is the "rapid" sleep phase that involves dreaming and completes the sleep cycle that occupies an average period of 90–100 minutes. There are usually 3 to 5 such cycles during night sleep. It is important to note that the complicated dynamics of EEG rhythms usually occurs in a state that was commonly regarded as functionally inactive, and can be characterized as a state of rest, inaction, and "generalized inhibition."

Additional complexities in the appraisal of the significance of the EEG are introduced by the fact that a particular rhythm can be observed in very different states of the brain. For example, apart from the state of drowsiness, the theta rhythm has also been found to be connected with emotional reactions (especially in children) and the problem-solving process.

Particular attention has been attracted by the fact that EEG rhythms and their considerable variability are largely connected with certain psychic states that, traditionally, have been studied in psychology (states of consciousness and unconsciousness, waking, dreaming, attention, emotion, learning and automatisation of action, etc.), rather than with the proposed local physiological events and regularities, even though the activity of the ensembles of brain nerve cells, i.e., physiological processes, has been recorded. More subtle phenomena in the human psyche, its content aspect, have not as yet been related to brain rhythms. The EEG patterns can hardly be regarded as patterns of thinking (see Ref. 10).

Practical applications of electroencephalography are founded on the relatively clear differentiation between brain rhythm patterns in different states of sleep and wakefulness (consciousness), and also normal and injured portions of the brain. The EEG has turned out to be an effective diagnostic and occasionally prognostic indicator in a number of brain pathologies, both focal (tumours, abscesses, traumas, and epilectic foci) and generalized (poisoning, disturbances in respiration and metabolism), in disturbed sleep, in various stages of surgical anesthesia, and as the result of the application of psychotropic medication.

The above facts clearly do not fit the picture that was generally accepted during the first half of this century and involved the so-called "dynamics of basic nervous processes", i.e., the processes of excitation and inhibition in the cerebral cortex during psychical activity.

However, the question remains as to what is the mechanism responsible for the electrical rhythms of the brain that would explain, from a unified standpoint, such properties as the extreme variability (mainly "microvariability") of outwardly uniform EEG patterns in states of wakefulness, their relative orderliness and diversity during sleep, the stability of the individual differences, the correlation with mostly psychological concepts, and our apparent inability in a number of cases to differentiate even between states of consciousness and unconsciousness on the basis of EEG patterns? A further question is why are these rhythms necessary to the brain? Certain approaches to answers to these questions will be presented in this paper.

c. Evoked potentials

Electrical brain waves are not the only spontaneous EEG rhythms. By using the techniques available for the

separation of signals from background noise, it has been possible to isolate a particular class of electrical macrophenomena in the EEG that are known as evoked potentials (EP). Evoked potentials take the form of short (~1 s) wave trains that are generated in the brain by a sensory stimulus, e.g., light, sound, contact with skin, and so on (when the stimulus is applied for a long period of time, the evoked potential will also appear on its removal). Since the exact time of application of the stimulus is known, it has been possible to develop the method of average evoked potentials in which the stimulus is repeatedly applied[11-14] in order to isolate evoked potentials of low amplitude (10–15 μV) from the "background" spontaneous EEG oscillations of substantially greater amplitude. The application of these techniques to other phenomena that can be accurately assigned to a particular instant of time, for example, the beginning and end of motion, expectancy and selection processes, and certain others, has demonstrated the existence of particular brain waves associated with these phenomena. Such waves and the sensory evoked potentials have therefore been combined in recent years into the group of event-related potentials (ERP). It will be important for our presentation to have information relating mainly to sensory evoked potentials, and we shall therefore now consider some of their general characteristics. Figure 3 shows typical evoked potentials produced by different brief stimuli and recorded from the scalp. The wave components of the EPs have different onset times (measured from the instant of application of the stimulus), and different phases and amplitudes. It is clear from Fig. 3a that the EP has an initial part that consists of oscillations of relatively low amplitude and high frequency, and continues for up to 50 ms. This is followed by a later stage that consists of slow waves with appreciably greater amplitudes and longer periods. The figure shows the EP recorded from a human subject, but an essentially similar picture is obtained for the main animal subjects (cat, dog, monkey).

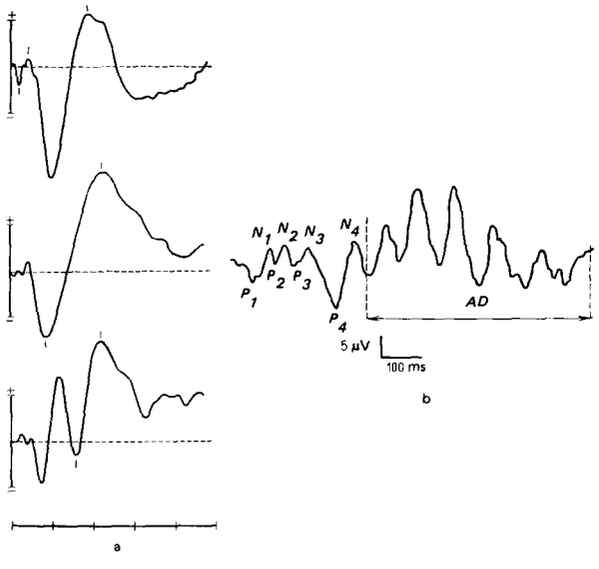

FIG. 3. a) Typical averaged evoked responses (with well-defined late components) to auditory (top), somatic (middle), and visual (bottom) stimuli[11]. Calibration: 100 ms, ±10 μV, positive upward. b) Averaged responses with afterdischarge evoked by a visual stimulus in the form a short (500 μs) flash of light. P_1, N_1, P_2, N_2, P_3, N_3, P_4, N_4—EP components (P—positive, N—negative), AD—afterdischarge.

It has been established that the initial part of the EP presents the direct response of neurons in the brain (including the cerebral cortex) to the arrival of impulses that appear as a result of the stimulation of sensory organs (receptors) and are transmitted along special sets of conductors through particular (relay) nuclei in the brain. This part of the EP reflects the physical characteristics of the applied stimulus, and is best defined in the zone of cortical projection corresponding to the particular type of sensitivity. The later relatively high-amplitude part of the EP that usually appears after a delay of 50–100 ms following the application of the stimulus is, to a considerable extent, connected with subsequent intracerebral processing of the arriving information that is directed toward the identification of the significance of this information (mobilization of attention, recognition of stimulus, evaluation of the probability of its appearance, and so on), acceptance of solution, and organization of new action (Fig. 4). This part of the EP is recorded over extensive cerebral territories and may appear even without the application of a stimulus, merely as a result of expectation that it will be applied (for example, when one of the stimuli in a regularly spaced series is omitted).[12-14]

There are data that can be used to associate late EP components with the activity of brain structures that are related to the generation of spontaneous EEG rhythms. This is indicated by studies of the so-called sensory afterdischarge which takes the form of a series of oscillations of the electric potential that appears with a delay of about 250 ms after the presentation of stimulus and continues for up to 1000 ms (Fig. 3b). In its frequency characteristics, the afterdischarge replicates the background EEG rhythm,[15] i.e., the alpha rhythm in waking states, the "dream spindle", and the theta and delta rhythms during sleep. We have recently confirmed this in an experiment (per-

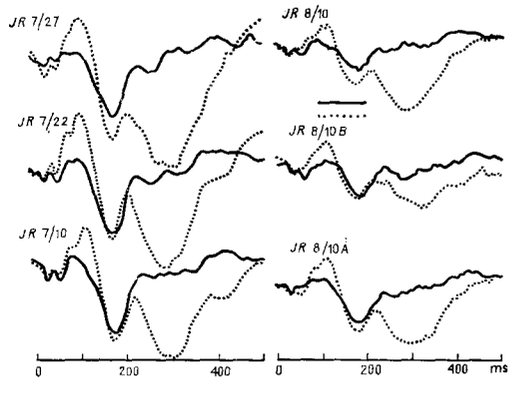

FIG. 4. Variation in the average evoked response for certain (solid lines) and uncertain (dashed lines) clicks. On the left, clicks had 25% probability of occurrence, on the right, clicks had 50% probability of occurrence.[11] Electrodes vertex to earlobe.

formed in collaboration with R. Biniaurishvili) in which an analysis of the EEG spectra has shown that the amplitudes of the afterdischarge waves increase with increasing spectral power density within the alpha-rhythm band corresponding to the same EEG segment of a subject in a state of wakefulness. This connection did not depend on the definition of the background alpha rhythm, since it was found to remain under the conditions of desynchronized EEG due to intense mental activity. It follows that the external stimulus producing the EP with an afterdischarge emerges as a factor that triggers the activity of the rhythm generators. There is a close connection between the individual characteristics of the spontaneous EEG and the character of the EP response to single infrequent stimuli and stimuli repeated at intervals in the EEG rhythm range.[16,17] In the latter case, the recorded EPs are so similar to the corresponding EEG rhythms that the phenomenon has been referred to as "EEG tracking" of the rhythm due to external stimuli. Strong direct correlations have been found between the sensory afterdischarge, which to a considerable extent, replicates the frequency of the spontaneous EEG rhythm, and the EP component that precedes the afterdischarge.[18]

The above data were obtained as a result of studies on humans, and most of them were repeated on animals. Apart from confirming the considerable generality of brain mechanisms responsible for the generation of spontaneous EEG rhythms and late EP components, they indicate that there is no clear dividing line between spontaneous and evoked activity. It is clear that, under realistic life conditions, the recorded EEG is the product of interference between both types of activity with interaction between their mechanisms which takes place mainly during times corresponding to late EP components. It appears that any perceived external event and any internal psychic excitation will give rise to characteristic shifts of the electrical potential (ERP) that cannot be isolated from the "background" of spontaneous EEG rhythms because there is no fixed point of origin or regular repetition. This suggestion is supported by experiments in which the subject was presented with a repeating pseudostochastic series of light stimuli of considerable duration. EEG segments of duration in excess of 3 s were then used to select complex EPs of comparable duration and statistical characteristics closely similar to the applied series of stimuli.[19] EPs have also been obtained in response to complete phrases, and it was found that there was a correlation between the amplitudes of the components, on the one hand, and the time distribution of acoustic pressure and the degree of phrase recognition on the other.[20] It is clear that the contribution of the relatively low-amplitude EPs to the total EEG can be manifested not only as a superposition on spontaneous oscillations but (and this is more important for our purposes here) as a change in the mechanism generating these oscillations.

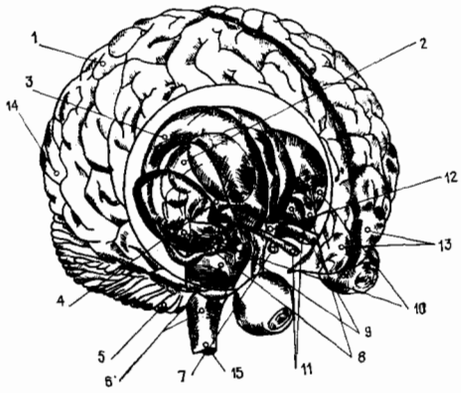

FIG. 5. Semischematic illustration of the human brain, showing its principal components. The cortex with the underlying white matter is shown separated from and raised above the subcortical structures. Deeper lying formations are shown through the circular "windows". 1—cerebral cortex 2—thalamus (interbrain), 3—caudate nucleus (subcortical nuclei), 4—midbrain, 5—cerebellum, 6—pons Varolii (above) and myelencephalon (below), 7—hypophysis, 8—hippocampus (part of limbic system), 9—amygdala (subcortical nucleus of the limbic system), 10—putamen and globus pallidus (subcortical nuclei which together with the caudate nucleus form the morphological complex—the striatum), 11—olfactory bulbs, 12—hypothalamus (interbrain), 13—frontal lobe cortex, 14—occipital lobe cortex, 15—brainstem (transition to myelencephalon).

d. Terminology and concepts referring to the structure and function of the brain and the neuron

1) *The brain.* Figure 5 shows the general appearance of the brain.[3)] Of the numerous structures shown in this figure, the formations identified in the sagittal section through the brain, shown in Fig. 6, are of particular relevance to the questions discussed here. These formations include the cerebral cortex, the thalami, which occupy a central position in the brain, the reticular formation of the brainstem, and the numerous massive connections between these formations. The reticular formation (RF) is located in the central part of the brainstem (Figs. 6 and 10) and runs along practically its entire length. The name derives from the netlike interlacing of processes of the constituent nerve cells.

Anatomically, the brain presents a symmetric structure of paired formations (cerebral and cerebellar hemispheres, thalami, subcortical nuclei, and so on; see Fig. 5). However, very considerable functional

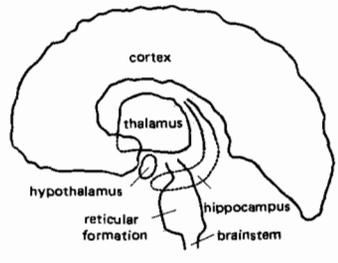

FIG. 6. Relative disposition of parts of the brain in medial saggital plane[21].

[3)] The brain and the spinal cord form the central nervous system (CNS).

differences have been established between the right and left hemispheres. These are related to the way information is processed in the two hemispheres, so that one can now speak of a different specialization of their activity.[22,23]

The gray matter of the brain is an accumulation of nerve-cell bodies and dendrites.[4)] The RF, the different nuclei of the brain, its cortex, the nuclei and cortex of the cerebellum, and the central part of the spinal cord consist of this material. The white matter of the brain consists of an accumulation of long, thread-like processes (axons) of brain cells that conduct impulses from cells and their clusters (nuclei) to other cells and clusters, and from the periphery of the nervous system to the brain, and vice versa. The two hemispheres are connected by a system of conductors (white matter), the principal mass of which forms the corpus callosum (the largest commissure of the brain). Portions of the cortex located on each of the adjacent inner surfaces of the hemispheres and lying in direct contact with corpus callosum, which they surround in an almost closed arc, are referred to as the limbic system which also includes the hippocampus (the old part of the cortex of the hemispheres in the evolutionary sense, in contrast to the neocortex which makes up the pallium) and certain other nuclei of the anterior brain, the hippothalamus and the thalamus (Figs. 5 and 6).

The brain is commonly subdivided into systems whose function is to transfer and partially process sensory information (visual, auditory, gustatory, olfactory, and information from skin and muscle receptors) to the so-called projection areas of the cerebral cortex, and systems that transmit commands from the cortex (from the motor areas) to motor neurons in the stem and the spinal cord, and from the latter to the muscles that execute motion. These systems are commonly referred to as "specific." It is important to note two points: 1) the projection areas in the cortex (sensory and motor) are only the effective inputs and outputs involved in information transfer and partial processing, and the deliverers of instructions, but are not the "higher centers" responsible for such functions which, to a considerable extent, are performed by the brain as a whole, using a wide range of different operations for current problem-solving with a hierarchical system for evaluating their relative importance, 2) the entire stream of sensory information arrives at the projection areas of the cortex after necessarily passing, with interruption, through particular thalamic nuclei which are specific to each type of sensitivity (the so-called specific nuclei), and 3) for certain involuntary actions, the processing of the "specific" sensory stream and the triggering of motor commands can occur in brainstem nuclei and even in the spinal cord.

There are also other systems that can be conventionally defined as organizing, monitoring, and regulating, i.e., self-organization systems for the brain as a whole. These systems consist largely of brain structures located near the brain axis, i.e., the RF of the brain stem, the central nuclei of the thalamus, the hippothalamus, the limbic system, and, to a considerable extent, the cerebellum, the subcortical nuclei, and areas in the cerebral cortex that lie between projection areas and are therefore referred to as association areas (frontal lobe and the region of contact between the parietal, occipital, and temporal lobes). Since these brain structures receive information from all the sensory organs and regulate all types of activity, so that their activation is reflected elsewhere in the brain, they are commonly referred to as "nonspecific." They have extensive bilateral connections both with each other and with all branches of the "specific" systems, which shows clearly that this subdivision is somewhat arbitrary.

"Nonspecific" formations in the brain play a decisive role in the appearance and maintenance of states of wakefulness and sleep, in satisfying primary needs of self-preservation, hunger and thirst, preservation of the species, search for new information (curiosity), organization of instinctive behavior, coordinated activity of internal organs (visceral, vegetative, systems), emotional experiences (both positive and negative), and control of memory. It will be shown in detail below that, in the final analysis, the origin and dynamics of EEG rhythms are connected precisely with the active state of "nonspecific" systems.

Naturally, the operation of the brain as a whole, involving, as it does, the evaluation of priority of objectives, problems, and organization of purposeful, i.e., fundamentally active (as was shown by Bernshteĭn;[24] see also Ref. 25) behavior is assured by the functional unity, i.e., continuous interaction, of all the "nonspecific" and "specific" brain formations and their systems.

2) *The neuron.*[5)] A nerve cell consists of a body (soma) and two types of process (Fig. 7). The body of the neuron contains a nucleus and certain other microorgans of the cell, and ensures matter and energy

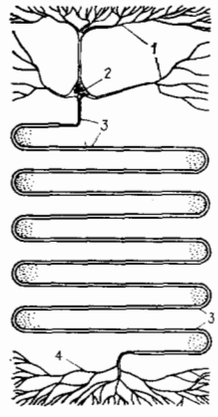

FIG. 7. Schematic diagram of the structure of the nerve cell (the neuron) in the case of the so-called pyramidal neuron in the cortex: 1—dendrites, 2—soma (body) of the cell, 3—axon, 4—axon terminals; axon hillock is located in the region where the axon leaves the soma.

[4)]Nerve cells will be described later.

[5)]A detailed discussion of the neuron can be found in Refs. 26–28.

transfer processes that lie at the basis of life. Growing out of the cell, there is one transmitting process, the axon,[6] which can range in length from 1 mm to some tens of centimeters and, by branching out, transmits electrical signals (impulses) generated by a particular zone of the cell soma (the axon hillock) through fine end twigs (terminals) to points of contact between the latter and other neurons. These points of contact—the synapses—are complex formations consisting of the terminal of the axon, the receiving membrane of another cell, and the gap between them. The transformation of the electrical signal into a chemical signal takes place in the synapse (in the so-called presynaptic part of the synapse), the structure of which has been investigated in detail with the electron microscope. The chemical signal in the form of a specific material (transmitter) is released into the synaptic gap and acts on special receptors in the membrane of the post-synaptic part of the synapse, thus modifying its ion permeability. The appearance of ion currents (due to the presence of electrochemical gradients) leads to changes in the charges on both sides of the membrane, i.e., an electrical signal is again produced that can be recorded by microelectrodes placed closely to the cell or introduced through the membrane into the interior of the cell. Each single neuron transfers its impulse to many nerve cells, each of which carries a large number (of the order of one thousand) of synapses. The assembly of axons emerging from many neurons form the conducting pathways in the interior of the brain and the peripheral nerves. The tree-like processes growing out of the neuron—the dendrites—of which there are usually several, are relatively short (up to 1 mm) and are looked upon (together with the soma) as the cell apparatus designed exclusively for the reception and processing of external influences (impulses) originating from other cells. Most of the synaptic mass is confined to the dendrites and soma. Depending on localization and origin, synapses are subdivided into axodendritic (transmission of impulse from axon to dendrite), axosomatic, and axon-axonic (from one axon to the endings of another axon). However, other types of synapse have been established in the central nervous system in recent years; namely, dendrodendritic (between dendrites of two neurons), dendrosomatic, and somatosomatic, forming a kind of microcircuits in the brain.[29] The spatial proximity of the dendrites and the bodies of different neurons then raises the question of a possible direct electrical interaction between them, without a chemical intermediary. On the other hand, when the separation between these components is of the order a few tens of microns, this interaction is problematic because of the rapid attenuation of the electrical signal. Special synapses with electrical rather than a chemical mechanism of transfer have also been discovered.

Depending on the synaptic action, neurons can be divided into excitatory and inhibitory. The former activate (through their axon and its branchings) the excitatory synapses on a receiving neuron, the latter activate the inhibitory synapses. Because of the difference in the concentration of anions and cations inside and outside the neuron, its enclosing membrane is polarized so that the material in the interior of the cell carries a negative charge relative to its exterior, with the result that, in the quiescent state, there is a potential difference of about 70 mV. Inhibitory effects give rise to the hyperpolarization of the membrane, whereas excitatory effects to its depolarization.

As far as the mass of gray matter (cortex and brain nuclei) is concerned, the neurons are commonly subdivided into three groups, namely, 1) those that transmit along their axons information to central nuclear formations, mainly from the different branches of sensory systems, but also from other nuclei; these are the afferent (bringing inward) neurons; 2) those that transmit from the cortex and from different brain nuclei commands addressed to the motor apparatus or other nuclei; these are the efferent (carrying outward) neurons; and 3) those that transmit information in the interior of a given nuclear formation without the emergence of axons outside its limits; these are the interneurons.

For the presentation that follows, it is very important to note that there are two qualitatively different types of electrical process that can occur in the neuron, namely, fast (of the order of 1 ms) and slow processes, where the latter can occupy periods of tens or hundreds of milliseconds. The former are traveling nerve impulses ("spikes," action currents) that are generated in the axon hillock on the body of the cell according to the "all or nothing" law in response to above-threshold stimuli and propagate along the axon without attenuation but with the amplitude of the spike being directly related to the diameter of the fiber. Repeated generation of spikes is possible but only after a definite refractory period (absolute and then relative) which continues for up to about 1 ms. Slow processes are generated by the subsynaptic membrane (or by a special auto-generation mechanism when the neuron is capable of generating spontaneous rhythms). They are gradual and propagate with attenuation along the membrane of dendrites and soma (there are some data indicating also attenuation-free propagation of current along a dendrite toward the body of the cell). These are referred to as post-synaptic potentials and can combine both in space and in time, which is seen as a reduction or an increase in the electrical polarization of the membrane. A reduction in polarization in the region of the axon hillock to the critical value (threshold) leads to the generation of a nerve impulse, i.e., a rapid oscillation in the potential. Thus, the slow potential oscillations reflect processes involved in the reception by the cell (its soma and dendrites) of arriving information and its integration, whereas fast oscillations are output commands that result from this. Since neurons are surrounded by a conducting medium, extracellular currents appear when a potential difference is set up between different portions of the cell (for example, between a dendrite and the soma or between different segments of the axon).

[6] The term axon is also used for the long process conducting the stimulus from the receptors of the sensory organs to the body of a neuron.

e. Connection between EEG waves and processes in individual brain neurons

Comparison between the EEG, recorded from the surface of the brain with the aid of large electrodes, and the activity of individual neurons located in brain tissue immediately below the surface, has shown that EEG waves are the result of a superposition of the slow activity of hundreds of thousands or even millions of neurons in the neighborhood of the large electrode. This isolates the activity of the part of the neuron population that acts in synchronism. For the appearance of EEG waves on the surface of the brain, it is sufficient to synchronize the activity of only 10–20% of neurons in this population, so that each individual neuron can either enter the synchronous activity or leave it, having been replaced by another.[30] The amplitude of the EEG waves is a measure of the number of neurons involved in the synchronous activity. Two cardinal concepts in EEG dynamics follow from this, namely, synchronization, i.e., an increase in the amplitude, and desynchronization, i.e., a reduction in the amplitude down to the disappearance of rhythms that can be distinguished by the eye (compare tracings I and II in Fig. 2).

It has been established that the slow activity that results in the EEG waves is a reflection of post-synaptic potentials. The synchronous fast (impulse) processes in neurons do not directly participate in its formation.

A factor that favors the summation of synchronous slow potentials and, consequently, the appearance of EEG rhythms is the same spatial orientation of enormous neuron populations. The cerebral cortex is characterized by the radial orientation of pyramidal neurons (in which the body of the cell has the form of a pyramid) with the apex of the pyramid and the uppermost dendrite (Fig. 7) pointing toward the surface of the brain whilst the base of the pyramid and the axon leaving it face the interior. It has been established that such radially oriented neurons form an ensemble in the cortex and respond in the same way to incoming stimuli (from sensory organs or other parts of the brain). These are the so-called cortical columns that form special functional units, referred to as micromodules.[31,32]

Physiologists differ on the question whether the EEG rhythms are only indicators of processes developing in large neuron populations or whether they play some independent role in the mechanisms involved in brain activity, thereby affecting the working properties of neurons. Until recently, most researchers tended toward the first point of view, but the discovery of very close contact between dendrites and the bodies of neighboring neurons with the formation of microcircuits must be acknowledged as admitting the possibility of the second suggestion.

2. MODELS OF THE GENERATION OF EEG RHYTHMS

a. Brain mechanisms controlling the appearance and dynamics of EEGs (physiological prerequisites)

The basis for these mechanisms lies in the important discoveries in neurophysiology that were made in 1940–1960. The following three discoveries may be regarded as the most important. They are of fundamental importance for the problem of brain activity, and the internal connection between them can be established quite clearly.

The first is related to the evaluation of the possibility that neurons in the cortex of the cerebral hemispheres (neocortex) can generate spontaneous rhythms. Burns[33] investigated the electrical activity of isolated cortical slabs (produced by cutting all neural connections but retaining sufficient blood supply) in an experimental animal (cat), and showed that neuronal elements of the cortex (chains or circuits formed by the neurons) were not themselves capable of prolonged generation of rhythmic oscillations in the potential. Electrical activity attenuates rapidly and spontaneously in such cortical regions in the absence of additional stimulation, and does not reappear. The application of an electrical stimulus above a certain threshold produces electrical activity in the isolated cortex, which takes the form of a neuronal pulse discharge (which is an indicator of continuing life activity of the neuron) and a slow wave recorded from the surface (Fig. 8). The activity propagates through the cortical slab with a velocity of about 20 cm/s. Damped oscillations of about 2 Hz follow for a period of 2–5 s, and "silence" returns thereafter. In prolonged experiments with the isolated cortex, the lesion that develops on the boundary of an incision can give rise to the stimulation of adjacent neurons and this in turn simulates spontaneous activity in the form of irregular groups of waves of about 2 Hz and, occasionally, discharges similar to epilectic discharges.

All this has given rise to the natural suggestion that rhythmic EEG activity is produced in the cerebral cortex under the influence of incoming rhythmic influences from other parts of the cortex. For this reason, we may consider that the second important discovery is the identification of special drivers of rhythmic activity or, in the language of physiologists, pacemakers (oscillators that drive the rhythmic activity). Electrodes inserted into the brain, including microelectrodes capable of recording local activity at different points in the brain and of individual neurons, have been used to show that such oscillators are largely concen-

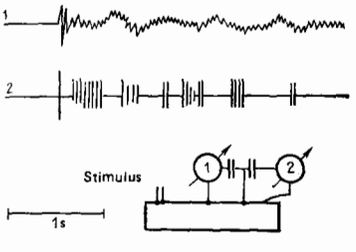

FIG. 8. Electrical activity of an isolated cortical slab (produced in cat by undercutting a section of the cortex so that it is not connected neurally to any other region of the brain) in response to a single irritation by an electrical shock.[33] 1—slow waves recorded from the surface of the isolated slab, 2—impulse activity of neurons in the interior of the slab. Experimental arrangement is shown at bottom.

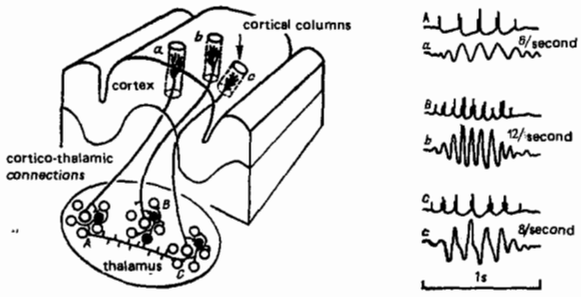

FIG. 9. A scheme for the interaction of thalamic pacemakers (oscillators) with each other and with functional units in the cortex.[34] Neutrons in thalamic oscillators A, B, C of different natural frequency and the cortical columns coupled with them and forming specially organized populations of cortical neurons (a, b, c). On the right, we show the corresponding recorded electrical activities of groups of thalamic neurons (obtained with inserted electrodes) and the EEGs of cortical regions. There is a characteristic relationship between pulsed neuronal discharges and slow waves. Open circles (thin line)—excitatory neurons, filled circles—inhibitory neurons, open circles (thick line)—output thalamic neurons (excitatory and inhibitory), directly coupled to the cortex and transmitting the influence of the thalamic oscillators. The reaction of the cortex is not shown.

trated in thalamic nuclei in the brains of the higher animals.[34-38]

The oscillators in thalamic nuclei can generate rhythmic activity when either the inflow of pulses from sensory organs and lower stages of the central nervous system is turned off, or after the neocortex is removed.[34,35] These data were obtained in experiments on cats in connection with "barbiturate spindles" (i.e., spindle-like bursts of waves of frequency 16–18 Hz during narcosis) and brain rhythms in an unanesthetized animal in the state of wakefulness or sleep (A, B, C on the right-hand side of Fig. 9). The right and left thalami, which are closely connected both anatomically and functionally, contain something of the order of 10^4 individual oscillators. They differ in wave repetition frequency, topography of projections on the cortex, and position in different thalamic nuclei. Most of the oscillators are located in nonspecific thalamic nuclei and a smaller proportion is found in specific (relay) nuclei. Figure 9 shows (on the left) a scheme illustrating the interaction of thalamic oscillators with the cortex, and the interaction between different parts of the thalamus. A direct demonstration of the dependence of the rhythmic spindle-like activity in the EEG of an animal on the activity of thalamic oscillators is the fact that it vanishes in one of the hemispheres when conductors between the thalamus and the cortex of the *same* hemisphere are unilaterally cut but are retained in the cortex of the other hemisphere; the activity disappears completely after experimental destruction of both thalami.[37]

The presence of a great variety of connections within the thalamus, both between its nuclei and within these nuclei, leads to the synchronization of the activity of many oscillators, especially those with similar natural frequencies, so that the number of effective pacemakers is much smaller (approximately 400). In addition, they can be subdivided into alpha, beta, theta, and delta groups, depending on the EEG frequency range. The rhythmic activity of the thalamic oscillators is transmitted by a volley of pulses to the corresponding zones of the cortex, possibly to functional units such as uniformly responding columns of neurons or sets of such columns. The rhythmic-wave response of the cortex in this type of epicenter of thalamic influence can propagate through the cortex for short distances through the intracortical transmission system.[39]

The third outstanding achievement in brain physiology, which is directly related to spontaneous EEG rhythms and their regulation, and also provides us with a way of recording them, has been the discovery of the function of a particular system of neurons that are part of the reticular formation (RF) of the brainstem (see Fig. 6) in which nonspecific thalamic nuclei can be considered to be the highest components.[21]

It was discovered that stimulation of the reticular formation by an electric current of frequency corresponding to the beta-range (or higher) through adapted electrodes gives rise on the EEG to the desynchronization (activation) reaction with a sharp reduction in the amplitude of spontaneous oscillations, a departure from their regularity, and the predominance of waves of higher frequency. A complex of changes appears that is practically identical to that observed during natural awakening of an animal, the onset of active wakefulness in man (Fig. 2, transition from 2 to 1), mobilization of attention, or emotional experience. Both destruction of midbrain RF and its isolation from the higher parts of the brain was found to lead to enhanced rhythmic activity on the EEG, the appearance of spindle-like bursts and/or slower oscillations of the potential, and to the prevention of desynchronization reactions in the presence of influences that usually give rise to such reactions, namely, pain stimulation of the skin or internal organs and arrival of unexpected meaningful signals through sensory organs.

As already noted, signals from all sensory inputs enter specific thalamic nuclei at some stage in their transmission and processing, and are thence directed to the corresponding zones in the cerebral cortex. However, even when this system of ascending transmission of signals remains intact whilst the RF is artificially destroyed, this does not ensure that the activation reaction will occur on the EEG under sensory stimulation, although the arrival of a signal in the cortex in the form of EP waves can actually be recorded. It is clear that the desynchronization of EEG rhythms requires the "sinking" of sensory signals in the RF of the brainstem, which modifies the activity of its neuronal system. Indeed, it has been established that, at all levels of the CNS, but especially in the brainstem, the sensory stream, i.e., the transmission of information from sensory organs along conducting brain pathways in the form of a sequence of nerve pulses, undergoes a bifurcation or duplication (Fig. 10). In addition to the flow of pulses along specific sensory systems (visual, aural, etc.), there is a second flow that is maintained by impulse volleys that arrive at

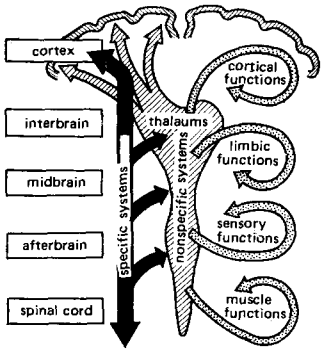

FIG. 10. Bifurcation of the stream of nerve impulses into specific (black area) and nonspecific (shaded area) components in the brain, showing the branching of specific pathways to nonspecific RF zones in the brainstem and the interbrain.[21] The influence of the latter on different functional systems in the brain and the associated feedback are shown.

the RF from the same sensory system along special branchings (collaterals) and modify its state. This manifests itself in changes in the character of spontaneous rhythms that are seen all over the surface of the cortex or in major portions of it. Complete desynchronization of the EEG is the extreme expression of such changes. This second ascending system has been called the "nonspecific" activation system. To a considerable extent, it acts through the "nonspecific" thalamic nuclei. The influence of the RF on the functional elements of the cortex, which does not proceed via the thalamus, is also known to play a significant role. It was shown subsequently that, apart from signals from sensory systems, the RF also receives a multitude of signals from other parts of the brain, namely, the neocortex, the limbic system, the subcortical nuclei, the cerebellum, and so on, as well as signals due to chemical factors circulating in blood. These are obviously related to changes in the spontaneous EEG rhythm due to the dynamics of higher brain processes, such as emotional experiences, thinking, organization of new activity, and so on. In many cases, the sensory stream might not change, i.e., there may be no obvious connection with events in the external world. This is exceedingly important because it indicates that there is no one-to-one correspondence between RF activity and its influence on thalamic oscillators, on the one hand, and the character of the sensory stream, on the other hand, the effect of which may vary substantially as a result of the arrival in the RF of impulses from other brain formations. Consequently, the RF activity is subject to central control that is also responsible for the selectivity with which signals are received in accordance with their significance.

A number of hypotheses have been put forward in connection with the functional significance of the separation of the stream of information arriving in the brain. They emphasize the activity of the ascending reticular activation system as a factor in the adjustment of other systems in the brain to developing specific activity. This includes the excitability of neurons, individualization of their activity as a result of desynchronization, and so on.[40,41]

For the ensuing discussion, it is essential to note that one stream proceeds along a specific system with practically no effect on spontaneous brain rhythms, whereas the other passes through the RF and the system of thalamic oscillators, and does change these rhythms.

The basic data relevant to the above three discoveries were obtained in studies on animals. There is every reason to suppose that they are also valid for man,[42] whose rhythmic EEG components are much more clearly defined than in animals. Direct confirmation of this is provided, in particular, by the absence of organized EEG rhythm in patients that have suffered damage to thalamic or lower-lying brain structures by a pathological process.[43,44] Such patients are in deep comatose condition (with loss of consciousness); their biological functions are maintained by modern critical-care methods, and their EEG exhibits low-amplitude activity dominated by slow waves of approximately 2 Hz and without any indication of organized rhythm. It would appear that, in such situations, the action of deep structures in the cortex is reduced to the irregular "firing" of functional units in the cortex by individual discharges, which produces attenuated oscillations, similar to those accompanying artificial stimulation of parts of the isolated cortex in experiments with animals. In other words, in man, the natural oscillatory properties of functional units in the cerebral cortex are largely analogous to those established by Burns in experiments with animals.

The foregoing facts have provided us with a basis for a fundamental theory of the nature of the interaction between thalamic nuclei generating the rhythmic activity and the neocortex, which takes into account all that is known about the dynamic properties of each of these parts of the brain. The essence of this theory is as follows. The oscillators formed by neurons in thalamic nuclei act on functional elements in the cortex by means of appropriately organized rhythmic volleys of impulses that are generated by them spontaneously. These cortical elements form the second oscillatory system that has the properties of a passive, highly nonlinear oscillatory circuit. Under normal conditions, this circuit cannot generate undamped, spontaneous, rhythmic activity. The natural frequency of the undamped oscillations (about 2 Hz) is much lower than the natural frequencies of the thalamic oscillators (pacemakers). There is evidence that the thalamus communicates with the functional elements in the cortex through the intermediary of interneurons, which are connected to oscillatory circuits in the cortex in such a way that this is equivalent to the injection of a potential oscillating at the frequency of the corresponding thalamic oscillators. The pacemaker properties of the thalamic oscillators and their interaction may change under the influence of the stream of pulses arriving from different parts of the brain and sensory organs which, in the final analysis, is reflected in changes in the activity

of the reticular formation in the brainstem, followed by direct action on thalamic oscillators.

b. Possible dynamic model of the generation of rhythmic electrical activity in the brain

We shall now try to describe the interaction between such major portions of the brain as the reticular formation, nonspecific thalamic nuclei, and different zones in the cortex in terms of a dynamic model involving a set of coupled, nonlinear differential equations. The solution of such equations should yield the oscillatory processes recorded on the EEG of a healthy brain in different states, and also in certain pathological states (for example, in epileptic seizures).

In this approximation, in each of these portions of the brain we can isolate zones that can be considered as functionally homogeneous ensembles of nerve cells (neuronial populations). Such ensembles will differ from one another by some specific features defining their operation. These differences will, hopefully, be incorporated in the above set of equations through the appropriate variation of their parameters.

Our discussion of the average interaction between excitatory and inhibitory neurons in the neuronal population will be based on the Wilson-Cowan model, which we shall adopt only for the purposes of illustration (and nothing else), but which is being widely used at present by both Soviet and foreign workers.[45-49]

Let us consider a somewhat simplified derivation of the equations in the Wilson-Cowan model. A more detailed and rigorous derivation can be found in the literature.[45,46,50] Consider a population of excitatory (e) and inhibitory (i) neurons coupled by excitatory and inhibitory links. For the initial variables characterizing the state of the neuronal population, we shall take the ratio of the number of active neurons (discharged by impulses) to their total number. We shall denote the variables by ρ_e and ρ_i, respectively. They may be considered as indicators of the average effect of synaptic activity in an isolated set of neurons. Since the excitatory and inhibitory neurons continuously interact, the variables ρ_e and ρ_i influence both the excitatory and the inhibitory neurons. It is exceedingly important to remember that the firing of a neuron (generation of an impulse) in response to an arriving set of impulses does not occur instantaneously, but is a certain function of time due to a set of processes characterizing the synaptic transmission (this is the time delay). The reaction of a neuron to a single excitation above the threshold value is therefore a relaxation function with a time constant τ_e, which represents the response to the message from the excitatory neurons, and there is a corresponding time constant τ_i for the inhibitory neurons. The time constants must be longer than the neuron firing time by one or two orders of magnitude (the former is of the order of 1 ms), so that they substantially exceed all other characteristic times, including the refractory time of a neuron after the generation of an impulse. Consequently, it may be considered that the post-synaptic potential decays exponentially between successive responses.

It is also assumed that the activities ρ_e and ρ_i are independent of coordinates in space. This is valid when the time taken by impulses to arrive at the synapses of neurons in a given population from other neurons in the same population is much shorter than the times characterizing the slow-wave (post-synaptic) process in neurons. Hence, the model equations for the ordinary and required variables involve only the time. They can be written in the form

$$\tau_e \frac{d\rho_e}{dt} + \rho_e = F_e(\rho_e, \rho_i), \qquad \tau_i \frac{d\rho_i}{dt} + \rho_i = F_i(\rho_e, \rho_i), \tag{1}$$

where F_e and F_i are certain functions (which may be referred to as reaction functions) that are determined on the basis of the following considerations. First, we must define conditions under which a neuron becomes active, assuming that the effects of exciting pulses arriving at synapses combine to produce a resultant function that exceeds some threshold, so that the activity of a neuron (generation of impulses) is determined by the resultant inflow from all the excitatory neurons interacting with the particular neuron over a time interval not exceeding τ_e. It may be considered that the synaptic effects of inhibitory impulses arriving from inhibitory neurons differ from excitatory effect by their sign. The resultant effect is thus determined by whether or not the resultant function of the post-synaptic potential exceeds the threshold at least once during the characteristic time.

To ensure that the neuron becomes active (generates an impulse), this resultant effect must reach the threshold value which we shall denote by Q_e and Q_i for the excitatory and inhibitory neurons, respectively.

There are four possible forms of coupling of each neuron to all others. 1) An excitatory neuron can be the target of a definite number of excitatory neurons. This type of coupling is represented by β_{ee}. 2) An excitatory neuron can be the target of inhibitory neurons. The probability of this type of coupling is β_{ei}. 3) An inhibitory neuron can be the target of excitatory neurons. The probability of this type of coupling is proportional to β_{ie}. 4) An inhibitory neuron is coupled to inhibitory neurons with a probability proportional to β_{ii}. All the β_{jk} have the dimensions of a potential. When they are reduced to dimensionless form, they are referred to as synaptic weights.

We shall now represent the activity of a neuron by a function of a linear combination of excitatory and inhibitory links in which it participates. The parentheses on the right-hand side of (1) will then acquire quantities corresponding to the presynaptic inflow and taking the form of the sum of presynaptic potentials $\varphi_e = \beta_{ee}\rho_e - \beta_{ei}\rho_i$ for excitatory neurons and $\varphi_i = \beta_{ie}\rho_e - \beta_{ii}\rho_i$ for inhibitory neurons. It is clear that the parentheses on the right-hand side of (1) should contain the following expressions:

$$\beta_{ee}\rho_e - \beta_{ei}\rho_i - Q_e, \quad \beta_{ie}\rho_e - \beta_{ii}\rho_i - Q_i. \tag{2}$$

However, these quantities have the dimensions of potential and are therefore not dimensionless. They can be made dimensionless by a suitable choice of the form of the functions F_e and F_i. This can be done as follows.

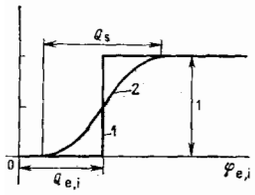

FIG. 11. See text.

As we know, each neuron fires (generates an impulse) in accordance with the "all or nothing" law, and this can be represented by the step function (Heaviside function) shown in Fig. 11 (curve 1). However, in reality, it is a certain set of neurons (neuronal population) that fires, and the effectiveness of the excitatory or inhibitory action in such populations is determined by the extent to which the average level of resultant excitatory inflow exceeds the threshold value $Q_{e,i}$. It is known that the neuron firing threshold can differ considerably in magnitude. It is also known that the reaction of a neuron population to an arriving influence can be described by a relationship that is close to linear within a certain range, when the influence is relatively small). When this is so, we can exploit the principle of superposition, i.e., the output will be proportional to the sum of inputs. As the strength of the action (φ) increases, nonlinear properties of the neuronic populations come into play and continue until saturation, after which further increase in the sum of presynaptic potentials does not lead to a growth in population activity. It follows that the actual dependence of the number of cells participating in discharges on the strength of the action that is external to the given population is of the form shown by curve 2 in Fig. 11. Curves of this type are referred to as logistic or sigmoidal and can be described analytically in a number of ways. The basic feature of curves of this type is the quantity Q_s (Fig. 11) which, in our case, is a measure of the spreading of the threshold values for the firing of neurons. Since Eq. (2) has the dimensions of a potential, it can be reduced to the dimensionless form by dividing it by the spreading of the threshold potential i.e., Q_{se} and Q_{si} in the case of excitatory and inhibitory neurons, respectively. Retaining the notation of (2), and remembering that all the quantities are now dimensionless, we can rewrite (1) in the form

$$\begin{aligned}&\frac{d\rho_e}{d\tau}+\rho_e=F_e(\beta_{ee}\rho_e-\beta_{ei}\rho_i-Q_e)=F_e(x),\\&\frac{d\rho_i}{d\tau}+\varepsilon\rho_i=\varepsilon F_i(\beta_{ie}\rho_e-\beta_{ii}\rho_i-Q_i)=\varepsilon F_i(x);\end{aligned}\tag{3}$$

where the time has been reduced to the dimensionless variable $\tau=t/\tau_e$ and we have made the substitution $\varepsilon=\tau_e/\tau_i$. Since physiological data indicate that the time constants for the inhibitory effects are greater than those for the excitatory effects, we have $\varepsilon<1$.

The logistic curve can be described by a number of different analytic functions. Wilson and Cowan and all subsequent workers in this field described this curve by the function $F(x)=1/(1+e^{-x})$ and performed subsequent calculations by numerical methods on a computer.

In this paper, we use a different expression, namely, $F(x)=(1/2)+(1/\pi)\arctan x$, which will also describe the logistic curve (the significance of this will be seen later). It is clear that, as $Q_{s,e,i}\to 0$, this curve becomes identical with the step function. The original equation can now be written in the explicit form

$$\begin{aligned}&\frac{d\rho_e}{d\tau}+\rho_e=\frac{1}{2}+\frac{1}{\pi}\operatorname{arctg}(\beta_{ee}\rho_e-\beta_{ei}\rho_i-Q_e),\\&\frac{d\rho_i}{d\tau}+\varepsilon\rho_i=\varepsilon\left[\frac{1}{2}+\frac{1}{\pi}\operatorname{arctg}(\beta_{ie}\rho_e-\beta_{ii}\rho_i-Q_i)\right].\end{aligned}\tag{4}$$

We shall now confine our analysis to the consideration of two cases: 1) oscillations in the system described by (4) in the absence of external disturbances will be considered with a view to finding the conditions under which the system will act as a pacemaker and 2) we shall examine forced oscillations of the neuronal population in the presence of a periodic external disturbance and try to determine the conditions for resonance and frequency division in the system, which will be important for our subsequent discussion.

The analytic expression that we have introduced for the logistic function which, as we have noted, is referred to as the reaction function in our case, can now be used to find an approximate analytic solution for the above problems. The functions ρ_e and ρ_i were written in the form $\rho_e=\bar{\rho}_e+\tilde{\rho}_e$ and $\rho_i=\bar{\rho}_i+\tilde{\rho}_i$, where $\bar{\rho}_e$ and $\bar{\rho}_i$ represent constant shifts of the working point and are found from the solution of the transcendental equations

$$\begin{aligned}&\bar{\rho}_e=F_e(\beta_{ee}\bar{\rho}_e-\beta_{ei}\bar{\rho}_i-Q_e)=F_e(\theta_e)=\frac{1}{2}+\frac{1}{\pi}\operatorname{arctg}\theta_e,\\&\bar{\rho}_i=F_i(\beta_{ie}\bar{\rho}_e-\beta_{ii}\bar{\rho}_i-Q_i)=F_i(\theta_i)=\frac{1}{2}+\frac{1}{\pi}\operatorname{arctg}\theta_i;\end{aligned}\tag{5}$$

where

$$\theta_e=\beta_{ee}\bar{\rho}_e-\beta_{ei}\bar{\rho}_i-Q_e,\quad \theta_i=\beta_{ie}\bar{\rho}_e-\beta_{ii}\bar{\rho}_i-Q_i.$$

The existence of a solution of this set of equations is the necessary condition under which oscillatory states are possible in the system (see also Ref. 50). The deviations from the constant (equilibrium) values, which will be denoted by $\tilde{\rho}_e$ and $\tilde{\rho}_i$, are obtained by solving the equations

$$\begin{aligned}&\frac{d\tilde{\rho}_e}{d\tau}+\tilde{\rho}_e=F_e(\theta_e+\beta_{ee}\tilde{\rho}_e-\beta_{ei}\tilde{\rho}_i)-F_e(\theta_e),\\&\frac{d\tilde{\rho}_i}{d\tau}+\varepsilon\tilde{\rho}_i=\varepsilon F_i(\theta_i+\beta_{ie}\tilde{\rho}_e-\beta_{ii}\tilde{\rho}_i)-\varepsilon F_i(\theta_i).\end{aligned}\tag{6}$$

We first find the solution of these equations in the linear approximation. The set of equations (6) then reduces to (the tildes are omitted)

$$\begin{aligned}&\frac{d\rho_e}{d\tau}+\rho_e=\frac{1}{\pi}\frac{\beta_{ee}\rho_e-\beta_{ei}\rho_i}{1+\theta_e^2},\\&\frac{d\rho_i}{d\tau}+\varepsilon\rho_i=\frac{\varepsilon}{\pi}\frac{\beta_{ie}\rho_e-\beta_{ii}\rho_i}{1+\theta_i^2}.\end{aligned}\tag{6a}$$

The roots of the characteristic equation for this system are $\mu=-\xi+i\omega_l$, where

$$\begin{aligned}&\xi=1-\frac{\beta_{ee}}{\pi(1+\theta_e^2)}+\varepsilon\left(1+\frac{\beta_{ii}}{\pi(1+\theta_i^2)}\right),\\&\omega_l^2=\frac{\varepsilon(\beta_{ei}\beta_{ie}-\beta_{ee}\beta_{ii})}{\pi^2(1+\theta_e^2)(1+\theta_i^2)}+\varepsilon\xi-\varepsilon^2-\frac{\xi^2}{4}.\end{aligned}\tag{7}$$

We shall now try to estimate these quantities on the basis of existing experimental data. According to Burns, the oscillation amplitude of elements in the cerebral cortex falls by a factor of l by the time $t/T\simeq 3$, where T is the period of natural oscillations of the cortical elements, so that the corresponding frequency is about 2.5 Hz. We then have $\tau_e\simeq 0.1$ s, which is

close to existing experimental data. In terms of our dimensionless variables, this corresponds to $\xi \simeq 0.2$ and $\omega_i \simeq 1.5$. This is the situation in the cortex. For thalamic rhythms, we have $\omega \simeq 4.5$ in the case of the theta rhythm, $\omega \simeq 6$ for the alpha rhythm, and $\omega > 10$ for beta rhythms.

It is clear from (7) that the damping of the system is determined by synaptic weights of a given form (β_{ee} and β_{ii}), whereas the frequency is determined by the cross-weights (β_{ei} and β_{ie}). Hence, it follows that the necessary condition for oscillatory states is $\beta_{ei}\beta_{ie} > \beta_{ee}\beta_{ii}$, which is also in agreement with experimental data. In order to avoid unwieldy expressions, we shall assume henceforth that β_{ii} is small in comparison with the other synaptic weights and will, in fact, assume in the calculations that it is equal to zero. This should have little effect on the qualitative results of our analysis, and there is no question of claiming that the precision of our quantitative relationships will be high. Our objective is to demonstrate the possibility of an analytic investigation of certain brain processes within the framework of the above model, and is in no way concerned with the derivation of computational expressions. Our concern is not so much with the model, but with the basic idea of a search for fractional resonances. Under these assumptions, the expressions given by (7) assume the much simpler form

$$\xi = 1 + \varepsilon - \frac{\beta_{ee}}{\pi(1+\theta_e^2)} \text{ and } \omega_i^2 \approx \Omega^2 - \varepsilon^2 + \frac{\xi^2}{4} \approx \Omega^2 - \varepsilon + \varepsilon\xi, \quad (7a)$$

where

$$\Omega^2 = \frac{1}{\pi^2}\frac{e\beta_{ei}\beta_{ie}}{(1+\theta_e^2)(1+\theta_i^2)}.$$

When $\xi > 0$, the state of equilibrium becomes unstable and the system may turn out to be capable of the generation of undamped oscillations whose amplitude is limited by nonlinearity. Such systems are the autogenerators or, as they are referred to in physiology, *pacemakers*. They are located in the thalamus and generate electrical oscillations that are transmitted to the cortex and are observed on the EEG or the MEG (electroencephalograms or magnetoencephelograms). However, the amplitude and frequency of these autooscillations can be found only by solving the nonlinear equations given by (5). To find the solution of (5), let us differentiate these equations with respect to time. Since

$$\frac{d}{d\tau}\operatorname{arctg} x = \frac{dx/d\tau}{1+x^2},$$

all the terms in the expressions obtained in this way involve rational functions, we have the possibility of obtaining reasonably accurate approximate solutions. This explains why we have taken the particular form for the reaction function. From now on, we shall use the methods developed in Ref. 51.

For our purposes, it will be sufficient to find the first approximation to the amplitude and frequency of the first harmonic component, i.e., we shall suppose that

$$\rho_e \approx \hat{\rho}_e \cos\omega\tau, \quad \rho_i \approx \hat{\rho}_i \cos(\omega\tau + \Delta\vartheta). \quad (8)$$

The determination of the higher-order approximations and the evaluation of the higher harmonic components present no fundamental difficulty although they do involve quite laborious calculations.

To avoid burdening the text with lengthy expressions, we shall not reproduce here the original equations and the relatively simple intermediate steps, especially since it is quite clear what these should be. We merely reproduce the final results:

$$\frac{\beta_{ee}^2\hat{\rho}_e^2}{4(1+\theta_e^2)} = -\frac{(1+\varepsilon)}{1+\omega^2},$$
$$\frac{\beta_{ee}}{\pi}\frac{\beta_{ie}^2\hat{\rho}_e^2}{4(1+\theta_e^2)(1+\theta_i^2)} = \left(\frac{\Omega^2}{\omega^2+\varepsilon^2} - 1\right)(1+\varepsilon) + \xi. \quad (9)$$

It is clear that the right-hand sides of these expressions must be positive. For the first of these expressions, this is a trivial result: equilibrium must be unstable for the autooscillatory system, i.e., $\xi < 0$, and the decay rate becomes a growth rate. To find the natural frequency of oscillations for this nonlinear oscillator, we eliminate β_e from these expressions. The frequency ω is then given by

$$\omega^2 - \omega_i^2 = \frac{\xi}{1+\omega^2}\left[\frac{(\omega^2+\varepsilon^2)\beta_{ie}^2}{\pi\beta_{ee}(1+\theta_i^2)} + \frac{(1+\omega^2)(\omega^2-\varepsilon)}{1+\varepsilon} + \frac{\xi}{4}\right], \quad (10)$$

and since $\xi < 0$, this means that the natural frequency of the oscillators decreases with increasing growth rate, as is usually the case for nonlinear oscillations. When $|\xi|/4\omega^2 \ll 1$ and $\omega^2 \gg 1$, which is valid for the thalamic autogenerators, we have

$$\omega^2 - \omega_i^2 = \xi\left[\frac{\beta_{ie}^2}{\pi\beta_{ee}(1+\theta_i^2)} + \frac{\omega^2}{1+\varepsilon}\right]. \quad (10a)$$

The upper solution in (9) shows that the amplitude of the oscillations is largely determined by the growth rate.

We have thus determined the basic characteristic features of the autogenerator described by the Wilson-Cowan type equations. It may be supposed that something similar is valid for the neuronal populations localized in particular structures of the thalamus. As far as quantitative estimates are concerned, these are hardly possible because, at present, we have no reliable information on the values of the parameters in these expressions.

We now proceed to the following problem. Consider an oscillatory circuit in the cortex that is being acted upon by a thalamic autogenerator. The initial equations now become

$$\frac{d\rho_e}{d\tau} + \rho_e + E\cos\nu\tau + \bar{E} = F_e(\beta_{ee}\rho_e - \beta_{ei}\rho_i - Q_e),$$
$$\frac{d\rho_i}{d\tau} + \varepsilon\rho_i + I\cos(\nu\tau + \eta) + \bar{I} = \varepsilon F_i(\beta_{ie}\rho_e - Q_i); \quad (11)$$

where E and I are dimensionless quantities representing the amplitude of the periodic action (excitatory and inhibitory, respectively) arriving from the thalamus and the cortex; η is the phase difference between the inhibitory and excitatory actions, and E and I are the corresponding constant components of the action of the thalamus on the cortex. When E and I are small, the linear approximation is valid and the solution contains two components, namely—natural, damped oscillations of frequency ω_i and decay rate ξ, and forced undamped oscillations of frequency ν. This is the general picture observed on the EEG for an adult person in a state

of quiet wakefulness, dominated by the α-rhythm if we ignore the amplitude and phase modulations similar to beats, which we shall consider later.

However, the situation may alter radically when the amplitudes of the external action (E and I) increase. Nonlinear effects then come into play and may lead to the appearance of resonance phenomena, including fractional resonances. This resembles the phenomenon of parametric resonance in linear systems, described, for example, by Mathieu-type equations, except that, in our case, the periodicity parameter changes as a result of nonlinearities in the system itself and not under the influence of external action. Such nonlinear parametric resonances (we shall refer to them as such) have been investigated in detail (see, for example, Ref. 51) and, despite the definite differences between the respective physical origins of these phenomena, and different methods of investigation, the basic general properties of the two sets of phenomena are quite close. Such systems exhibit an alternation of regions of stability and instability. Exit from a region of stability is accompanied by discontinuous change in frequency whilst the amplitude is determined not by external action but by the characteristics of the system.

At this point, we present a brief discussion of a fractional resonance involving frequency division by a factor of two, which is characteristic for particular pathological processes in the brain. This occurs during epileptic seizures of a certain type (see Section 3a) and in certain other pathologies, for example, in the tremor accompanying Parkinson's disease (see Section 3b). In particular, it will be seen in Section 3 that epileptic seizures are characterized by three types of resonance. Analysis of these situations is fundamentally no different from what we have given here, and we shall therefore not reproduce it.

We shall seek the solution of (11) in the lowest-order approximation for the first harmonic component in the form

$$\rho_e=\hat{\rho}_e\cos\left(\frac{\nu\tau}{2}+\vartheta_e\right)\text{ and }\rho_i\approx\hat{\rho}_i\cos\left(\frac{\nu\tau}{2}+\vartheta_i\right). \tag{12}$$

The first step is to apply the operation of differentiation to these equations. Further analysis will be performed by the methods described in Ref. 51, but it will be assumed that the system lies in the "neighborhood" of this type of nonlinear parametric resonance. This means that the "detuning" (a term commonly used in radioengineering in this context) is such that $(\nu/2-\omega)/\omega\ll 1$, i.e., we assume that this difference is small (ω is the natural frequency of the system of oscillatory cortical elements). Moreover, the attenuation ξ of the natural oscillations of the cortex is also assumed to be small. In subsequent calculations, therefore, we shall neglect all powers $(\nu/2-\omega)/\omega$ and ξ of degree greater than one (in the first approximation) and also products of these quantities. Near resonance, we shall assume, as is usually done, that the quantities E and I are also small.

Methods analogous to those described above can be used to show that, in the first approximation for the fundamental harmonic component, the relationship between the "detuning" and the external excitatory and inhibitory action is

$$E\sin 2(\vartheta_e+\gamma)=\frac{2\left(\frac{\nu}{2}-\omega\right)\theta_e}{(1+\omega^2)(1-3\theta_e^2)},$$
$$I\sin(2\vartheta_e-\eta)=\frac{2\left(\frac{\nu}{2}-\omega\right)\theta_i}{\Omega^2(1-3\theta_i^2)}, \tag{13}$$

and the condition for frequency division is obtained from the condition that ρ_e^2 must be greater than zero.

We shall not reproduce all the intermediate steps, and merely write down the result which reduces to the following inequality:

$$\theta_i^2(\omega^2-\varepsilon)^2I^2+\varepsilon^2\theta_e^2(1+\omega^2)^2E^2+2\varepsilon\theta_i\theta_e(\omega^2-\varepsilon)(1+\omega^2)EI\cos(2\gamma+\eta)$$
$$>\frac{\varepsilon^2}{(\omega^2+\varepsilon^2)(1+\varepsilon)^2}\left\{4\left(\frac{\nu}{2}-\omega\right)^2\left[\frac{\varepsilon^2\theta_i^2(\omega^2-\varepsilon)(1+\varepsilon)}{1-3\theta_i^2}+\frac{\theta_e^2(\omega^2+\varepsilon^2)}{1-3\theta_e^2}\right]^2\right.$$
$$\left.+\frac{(1+\varepsilon)^4}{4}\left[\omega\xi-2\left(\frac{\nu}{2}-\omega\right)\left(\frac{2\theta_i\varepsilon}{1-3\theta_i^2}-\omega^2+\varepsilon\right)\right]^2\right\}; \tag{14}$$

where γ is an angle introduced for the sake of convenience and given by $\cos^2\gamma=1/(1+\omega^2)$. The above approximation is, of course, valid only provided the quantities $|1-3\theta_e^2|$ and $|1-3\theta_i^2|$ are not too small (of the order of unity). It follows from (13) that both excitatory (E) and inhibitory (I) action by the thalamus is necessary for the compensation of the "detuning." The inequality given by (14) is somewhat cumbersome, but its physical significance is quite clear. Similar expressions are always obtained in the solution of problems of this type. Our situation is complicated by the fact that, firstly, instead of the usual external action, we have to deal with two actions (E and I) and, secondly, we have taken the damping ξ into account.

It is interesting to note, at this point, that the Wilson-Cowan model can also have a solution with frequency division by a factor of three, and there have been recent reports that this phenomenon has been observed in animals under extreme conditions. In our model, this solution is possible, but E and I cannot then be considered small, as above. In the experiments with frequency division by a factor of three, these quantities were also quite large.

So far, we have confined our attention to single neuronal populations with particular oscillatory characteristics: they were either coupled to an external source with a periodically variable action, or they were functioning as a single generator of autooscillations. In reality, there are many such neuronal populations, and they continually interact with one another with different coupling strengths. When the coupling is relatively weak, the populations may be regarded as quasi-independent, and this was, in fact, done above. However, analysis of even two sufficiently strongly coupled neuronal populations, described by the Wilson-Cowan equations, has so far turned out to be practically impossible by the methods available to us. A numerical study on the BESM-6 computer of this case has been reported,[48,52] in which the values of β_{ee} and the coupling coefficient were varied.

It has been found that the solution of even this simple problem is such that depending on the chosen parame-

ter values, the system can support very different states, including synchronization, beats, multiperiodic states, and, finally, stochastic states. Beats and multiperiodic states are particularly interesting in connection with the general problems raised in the present paper.

Analysis of the EEG corresponding to the different states of man suggests that there are two different types of interaction between the oscillators, both inside the principal source of autooscillations, i.e., the thalamus, and with the oscillatory elements of the cortex. The EEG pattern recorded in quiet waking states or in states of normal activity (Fig. 2, II), with the well-defined main frequency oscillations (alpha rhythm) and amplitude modulation ("spindles"), can be interpreted as the interaction within the alpha-frequency range of several *auto-oscillatory devices*, slightly differing in their period, which is accompanied by the appearance of a frequency band with near-Gaussian distribution having a halfwidth of about 1 Hz. It is clear that interaction between a number of such oscillators will lead to amplitude and frequency-phase modulation similar to beats, but with the difference that the number of such generators is quite large and they have well-defined nonlinear characteristics. The alpha-rhythm spindles are therefore irregular in character, and their duration can vary within relatively wide limits. A similar stochastic self-modulation occurs[5] in certain problems in hydrodynamics. The spindle-like structure of the alpha rhythm can also have a regular character when it takes the form of a multiperiodic process whose pattern is reflected in the spindle envelope. The parameters of this process determine the transition from the harmonic to the stochastic state. The couplings between the individual oscillators within a given frequency range are than clearly such that the system has not yet reached the stochastic state, but has attained the periodic state. This type of process is completely in accord with modern ideas on the existence of intermediate states in passing from a periodic to a stochastic process (or, in the language of hydrodynamics, from a laminar to a turbulent flow). An intermediate state of this kind is a quasiperiodic process with an increasing number of harmonic components, depending on the size of the parameters defining it, for example, the couplings between the oscillators. The so-called Landau-Hopf bifurcations lie at the basis of the dynamics of such processes.

Ruelle and Takkens[1,53] have found that, after a few Landau-Hopf bifurcations, the system goes over into a stochastic state, in which the so-called strange attractor is found to appear. Since then, a number of other scenarios have been found for the transition of a dynamic system to a stochastic state, including the theory of Feigenbaum or Pomeau-Manneville (see, for example, Ref. 54). For our purposes, it is particularly important to know not only whether or not near-stochastic multiperiodic patterns can be set up in complex, dissipative, dynamic systems, but also the extent to which such patterns are sensitive to the application of noise-type signals to them. In 1974, Kifer (cited in Ref. 54) showed that dynamic systems with Ruelle-Takkens-type attractors are not sensitive to white-noise perturbations provided, of course, that the noise level is not too high. This result inspires the conviction that actions produced by neuronal structures are sufficiently stable and capable of carrying information undistorted by random perturbations. The fact that the spindle-like modulation of EEG rhythms is not a purely stochastic process, but is subject to definite determined regularities, is indicated by the stability of the individual EEG characteristics discussed in Section 1a. A similar explanation can be given for other types of spindle-like EEG rhythms, namely, the theta-rhythm and the beta-rhythm, including those recorded in states of sleep. In the last case, there is a definite stage in the development of sleep where a less regular thalamic oscillator action on the cerebral cortex leads to a more clearly defined delta rhythm that is due to the firing of cortical oscillatory elements at their natural frequency by infrequent thalamic impulse volleys.

There is particular interest in EEG patterns characterizing states of active wakefulness (see Fig. 2, I) and, at first sight, taking the form of a completely disordered sequence of low-amplitude waves in a broad frequency spectrum dominated by the higher frequencies. In the light of the ideas developed in this paper, this may signify a transition from interaction between thalamic oscillators within a given frequency band (for example, the alphaband) with synchronization ("trapping") phenomena, to the interaction between oscillators with different EEG frequencies (alpha, theta, beta, and, possibly, higher frequencies) with the desynchronization of the oscillations. It is possible that the predominance of the higher frequencies is due to interactions with oscillators in other deep brain structures (amygdala), whose natural frequency is in the range 25–60 Hz.

This kind of change in the interaction between oscillators with different frequency characteristics is due to stimuli arriving from the external world and to internal stimuli. Analysis of the EEG patterns corresponding to this type of interaction is exceedingly difficult because of their particularly dynamic character. To some extent, it can be performed under the conditions of artificial temporal stabilization, using the characteristics of late EP components. This will be discussed in detail in a later section (Section 3c).

To conclude this section, it is important to note that the utility of dynamic analogies for biological systems as complex as the central nervous system is limited not only by the lack of reliable values for measured quantities that would enable us to obtain at least crude estimates of the model parameters. At present, the memory mechanism, the type of record, the mechanism responsible for the "reading" of previously recorded information, and the very substrate on which this information is recorded are still unknown. Existing experimental data and conclusions based upon them do not appear to be sufficiently reliable. Under these conditions, analogies and illustrations are introduced to provide, at best, a qualitative and not inconsistent explanation of individual observations, to establish fun-

damentally common features, and, hence, map out the line of further research.

3. SOME ASPECTS OF BRAIN PATHOLOGY AND PHYSIOLOGY

a. On the mechanism of generalized paroxysmial EEG rhythms in certain types of epilepsy

Epilepsy is a disorder of the brain in which there is a sudden appearance of synchronous discharges involving an unusually large number of neurons (paroxysmal discharges) or a series of such discharges (paroxysmal rhythms). When such discharges encompass all the higher branches of the brain, namely, the cortex, the subcortical nuclei, and the midbrain structures of very large territories within it, i.e., when they become generalized, the resulting epileptic seizure is characterized by loss of consciousness, major convulsions of the musculature or stupor, or the appearance of complex and outwardly purposeful motor behavior in states of modified consciousness.[8] Seizure with instantaneous loss of consciousness and major convulsions is commonly referred to as grand mal. Loss of consciousness with generalized stupor, usually over a short period of time, is sometimes referred to as petit mal. Finally, seizure accompanied by automatism against a background of modified consciousness belongs to the category of psychomotor attacks. At the end of any of these seizures, the patient usually has no memory of what happened or of the length of the attack.

When the paroxysmal discharges occur in some restricted portion of the brain, the epilepsy is usually classified as focal. When there is no generalization to an extensive territory, the seizure may be characterized by local convulsions or sensory symptoms without loss of consciousness. It has been found that different forms of epilepsy have different manifestations on the EEG. The common feature is the sudden appearance of oscillations of modified frequency, which rapidly increase in amplitude above the common background. Examples of characteristic EEG patterns corresponding to different forms of epilepsy are shown in Fig. 12. The EEG manifestations of epilepsy have certain typical forms and this has resulted in electroclinical classification of epilepsies in the light of both clinical and electrographical indicators. Occasionally, brief EEG shifts are not accompanied by the onset of seizure. One then speaks of a subclinical seizure. In accordance with the inequality given by (14) (Section 2b), the transition from the normal EEG rhythm to the paroxysmal rhythm that is characteristic for generalized epileptic seizures may be due to either the enhanced action of thalamic pacemakers or an increase in the frequency of natural oscillations of the cortex. In either case, an increase in nonlinear effects may produce a sudden transition of the system to the generating state (in particular, a state involving the division of the frequency of the dominant oscillator group by a factor of two) and a sharp increase in the oscillation amplitude.

Such a system can also generate oscillations with other frequency characteristics. Further increase in

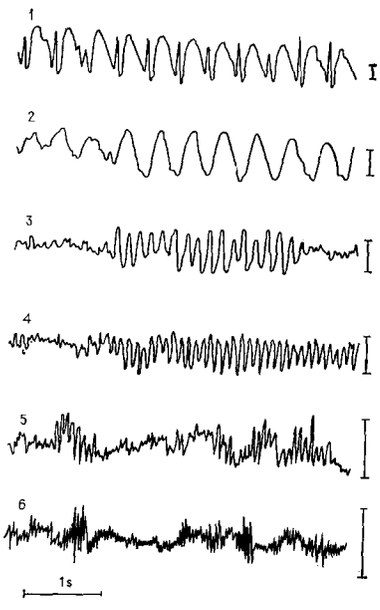

FIG. 12. Paroxysmal EEG rhythms in epileptic patients and in periods between seizures (subclinical discharges)[8]. 1—series of wave-peak complexes, 2—burst of delta waves (about 3 Hz in both cases), characteristic for cases of petit mal, 3—burst of 6-Hz waves (psychomotor seizure), 4–6—bursts of 10, 14, and 25 Hz waves (observed all over the brain in grand mal). Calibration: 1 s, 100 μV.

the amplitude of the stimulating action E and I due to the synchronization of thalamic oscillators or a reduction in the "detuning" as a result of an increase in the natural frequency ω_t in the neuronal populations of the cortex, may result in the excitation of oscillations with frequencies $\nu \simeq n\omega_t/2$; $n=1, 2, 3, \ldots$. When $n=1$, the frequency is divided by a factor of two.

If we now formulate the basic conditions for a transition from the normal EEG rhythm to the generalized paroxysmal rhythm encountered in epilepsy, we find they take the following form (see also Ref. 55). As already noted, it is assumed that normal rhythms result from the action of thalamic pacemakers on functional units in the cerebral cortex, which have the oscillatory properties of a passive circuit and reproduce (provided the intensity is high enough and the "detuning" is relatively large) the frequencies of thalamic oscillators (pacemakers) that are predominant under the particular specific conditions. The transition of these rhythms into the paroxysmal EEG rhythms may be due to an increase in the intensity of the rhythmic action of the thalamus (as a result of enhanced synchronization of pacemakers) or a primary malfunction of cortical elements due to different pathologic factors (lesion, brain tumour, abscess, damage to blood circulation, and so on) that enhance the excitability of these elements with increasing natural frequency of the oscillations. In the latter case, when this frequency approaches one-half of the thalamic pacemaker frequency, the system undergoes a sudden transition to the paroxysmal state that is analogous to the so-called first instability region on the Mathieu diagram, which is characterized by the divi-

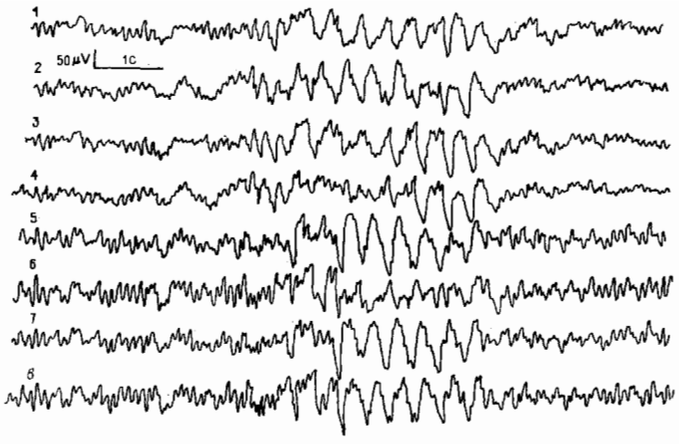

FIG. 13. EEG recorded from a 37-year old patient suffering from petit mal. Appearance of a discharge of 3-Hz waves in quiet wakefulness, preceded by a brief burst of 6-Hz theta-rhythm in frontal regions of the brain. Recordings: 1 and 2—frontal temporal, 3 and 4—central temporal, 5 and 6—parieto-temporal, 7 and 8—parieto-occipital bipolar. Here and in the next two figures, odd and even recordings correspond to right and left hemispheres, respectively. Calibration: 1 s, 50 μV.

sion of frequency by a factor of two, and a sharp increase in the amplitude of the oscillations.

Paroxysmal EEG rhythms have the following characteristic frequencies: about 3 Hz in petit mal, about 5 Hz in psychomotor seizures, and about 10, 15, and 20 Hz in cases of grand mal. Since the dominant normal rhythm in states of wakefulness is the alpha-rhythm, the above hypothesis provides a good explanation of the appearance of 5–6 Hz discharges on the EEG in psychomotor seizures (division of the alpha frequency by a factor of two, in accordance with the relation $\nu \simeq n\omega_1/2$, $n=1$), and about 10, 15, and 20 Hz in the case of grand mal ($n=2, 3, 4, \ldots$). However, the validity of the hypothesis would be better supported by data obtained *after* rather than *before* the prediction. Thus, for the hypothesis to be valid in the case of petit mal paroxysms with characteristic frequency 2.5–3.5 Hz, one would have to assume that the dominant frequency of thalamic pacemakers is, in this case, the theta-rhythm frequency (5–7 Hz) with $n=1$. To verify this assumption, a detailed analysis has been carried out of EEG recordings obtained in petit mal cases and a comparison was made between the conditions necessary for the appearance of the theta rhythm on normal EEG and in petit mal discharges.

The following facts and coincidences between the working conditions have been established:

1. A theta-rhythm burst appears on the EEG immediately before the onset of petit mal-type discharges. In Fig. 13, this type of burst preceded the paroxysmal discharge and concluded it in a patient in the state of quiet wakefulness. The same phenomenon may occur, as is clear from Fig. 14, at the beginning of the paroxysm during a transition from wakefulness to sleep. The regular enhancement of the theta rhythm in the region of the temporal cortical focus immediately before the generalized discharge of the ~3 Hz rhythm was confirmed by a special study using an analysis of EEG frequency spectra.[56]

2. Figure 15 illustrates a case where paroxysmal delta waves of about 3.5 Hz, which occasionally encompass only posterior areas of the hemispheres (B), were accompanied in anterior (central lobe) areas by a theta rhythm of 7 Hz. It may be considered that, in this case, the incomplete propagation of petit mal-type discharges over the cortex enables us to see the rhythmic action of thalamic pacemakers, which dominates the situation at this time and has a frequency that is higher by a factor of two.

These facts may be regarded as a direct confirmation of our hypothesis. However, there is also indirect evidence.

3. Cases of petit mal are more frequent in children

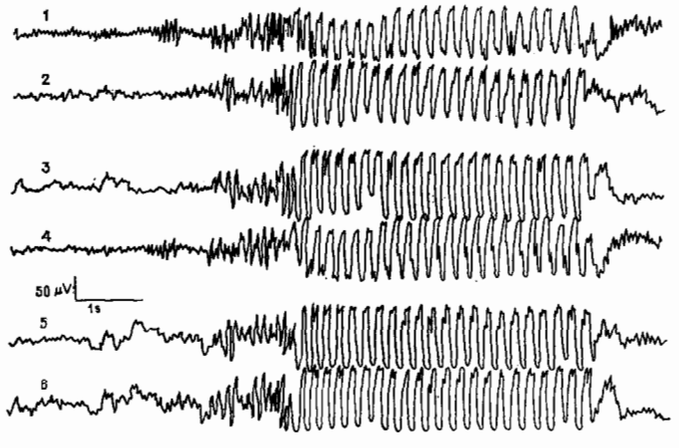

FIG. 14. EEG recorded from 13-year old patient suffering from petit mal. In the state of predormition (transition to stage 1 of sleep), the petit mal seizure was preceded by signs of theta-rhythm. Recordings: 1 and 2—occipital, 3 and 4—parietal, 5 and 6—monopolar frontal. Calibration: 1 s, 50 μV.

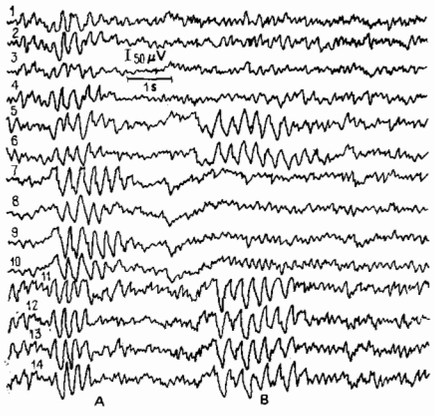

FIG. 15. EEG recorded from 5-year old patient suffering from petit mal. Generalized (*A*) and partial (*B*) subclinical discharges of 3–3.5 Hz delta-waves. A burst of 7-Hz theta-rhythm can be seen in centro-frontal region in the case of the partial discharge. Recordings: 1 and 2—central, 3 and 4—temporal, 5 and 6—monopolar occipital, 7 and 8—fronto-temporal, 9 and 10—fronto-central, 11 and 12—occipito-temporal, 13 and 14—bipolar parieto-occipital. Calibration: 1 s, 50 μV.

of 7-9 years,[57,58] for whom, even under normal conditions, the EEG is found to contain theta-rhythm bursts and, occasionally, delta waves similar to the manifestations of petit mal (possibly, frequency division in physiological and borderline conditions). As the alpha-rhythm increases and becomes established, petit mal terminates in many pediatric cases.

4. The connection between the onset of the theta rhythm and petit mal paroxysms, on the one hand, and particular sleep stages, on the other hand, which has already been noted above, is not accidental. Petit mal discharges frequently occur during transitions from wakefulness to "slow" sleep (in stage 1) and from "slow" sleep to "rapid" sleep.[59] Bursts of the theta rhythm usually occur precisely during these periods.[42]

5. Forced hyperventilation (deeper and more frequent respiration) is similar to the induction of sleep in that it is one of the usual devices employed to induce (for diagnostic purposes) epileptic discharges on the EEG. Such tests frequently transform background EEG activity in quiet wakefulness to the theta rhythm, even in adults.[60]

Thus, the above facts, and the connections between conditions for the appearance on the EEG of theta rhythms and the generation of petit mal-type discharges (frequency ~3 Hz), can be considered as a definite confirmation of the proposed hypothesis. It is possible that a ~5 Hz discharge during psychomotor seizures is also associated with the theta rhythm. In that case, the frequency is given by $\nu = n\omega/2$ with $n = 2$.

An interesting feature of the proposed scheme is that it can form a basis for resolving a dispute of many years' standing between Canadian and French epileptologists about the mechanisms responsible for generalized paroxysmal rhythms on the EEG. In the light of the proposed scheme, there is no point to this dispute since the two points of view are complementary rather than mutually exclusive (as is indicated by many facts).

The Montreal school considers that centrocephalic formations (i.e., those located deep in the center of the brain, mainly in the central nuclei of the thalamus) are the primary sources of generalized paroxysmal rhythms that are distinguished by strong, bilateral (involving the two hemispheres) synchronism. This possibility was demonstrated by direct electrical stimulation of central formations in midbrain.[8] In such cases, the critical intensity of the action of thalamic pacemakers on the cortex, which converts oscillatory elements in the cortex into generators of epileptic rhythms, can be reached in the case of relatively large "detuning." The transition to this state can also occur as a result of primary affection of the cortex, and the French school maintains that this is the leading factor. In that case, the enhanced excitability of cortical functional elements leads to an increase in the natural frequency of oscillations generated by them, and a reduction in the "detuning" down to values for which the normal rhythmic action of thalamic pacemakers is sufficient for the transition of the system to a pathological state. One can therefore understand reports that normal rhythm in the thalamus has been recorded in such cases at the same time as well-defined generalized paroxysmal rhythmic discharges on the cortical EEG.[61] The very rapid generalization of discharges under primary affection of the cortex can be explained by the close values of the oscillatory characteristics of its functional elements (about 2 Hz) in the presence of very intensive action by the epileptogenic cortical focus. Under these conditions, the interaction between the focus and adjacent cortical regions, in which they are "trapped" into the paroxysmal rhythm, is promoted by the same mechanism that underlies the interaction between the thalamic pacemakers and the cortex. This is facilitated by the combination of a reduction in the "detuning" and the increase in the intensity of the action from the focus.

b. Parkinson's disease

Regularities in the EEG of a human subject may also be characteristic of the dynamics of processes in other portions of central nervous system, This is exemplified by the tremor seen in Parkinson's disease, which produces a periodic activation (contraction) of muscles which gives rise to the tremor (Parkinsonism) of different parts of the body, namely, the extremities and the head. Even in the case of a healthy person, the maintenance of these portions of the body in a particular position involves an imperceptible oscillation about the maintained posture. This physiological tremor is a reflection of the operation of muscles in the course of active maintenance of the required posture (for example, when one tries to hold an outstretched hand in the horizontal position). This muscle operation involves the simultaneous application of relatively few opposing motor units, namely, a definite number of muscle fibers controlled by a single motor neuron. They are activated asynchronously with close frequencies in the 10-Hz range, and the oscillations are not strictly

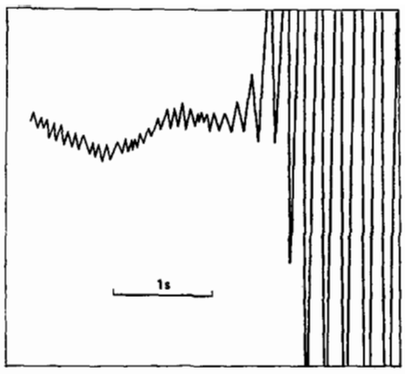

FIG. 16. Oscillogram of a tremor: transition from physiological to Parkinsonian tremor.

periodic (the ratio of the standard deviation to the mean is 0.2–0.3). This state of activation involves periodic grouping of impulses, so that the force developed by muscles displacing the limb in opposite directions is not constant, with one or other direction predominating, and this is eventually responsible for the physiological tremor.

In the tremor form of Parkinson's disease, the amplitude of the tremor increases by a factor of 30–100 and the frequency decreases by exactly a factor of two as compared with the frequency of the physiological tremor. Moreover, the oscillations become regular. This is clearly seen in situations where the physiological tremor is transformed into the Parkinsonian tremor and vice versa. Figure 16 shows an oscillogram of the variation in the angle of the radiocarpal joint when the hand is held in a particular position during this transition. The essential point is that the increase in amplitude, the division of frequency, and the onset of regular oscillations occurs suddenly without an intermediate state.

Various hypotheses have been put forward to explain this transition of the physiological into the Parkinsonian tremor (they include the hypothesis of the "central" generator of the tremor in the brain, the formation of a generator in the spinal column, and so on). In 1974, we put forward[62] the hypothesis that the Parkinsonian tremor was the result of a nonlinear parametric resonance, similar to that occurring during certain specific epileptic seizures (see above). One can then take as the starting point (using the appropriate terminology and concepts) the fact that the system controlling the activity of muscles, in effect, undergoes a transition from the first region of stability on the Mathieu diagram to an unstable region with the division of the frequency by a factor of two. This hypothesis provides a unified way of describing both the change in the frequency and the increase in the amplitude (which is determined not by the strength of external action but by the nonlinearity of the characteristics of the system) as well as the high regularity of the oscillations.

This hypothesis has recently received experimental confirmation by Japanese researchers.[63] Motor disorders such as Parkinsonism were induced in experimental animals (cats and monkeys) by destroying the black substance (one of the nuclei in the brain stem). Inserted electrodes were then used to record the electrical activity of the caudate nucleus, globus pallidus, and a number of other subcortical nuclei (Fig. 5) as well as the ventrolateral and central thalamic nuclei. They also recorded the electrical activity of muscles in different portions of the body, the motion of the eyes, and the usual EEG. These recordings were made in the course of "rapid" sleep when muscle tonus vanishes and the thalamus does not receive any signals from muscles. These studies have shown that the frequency of oscillations in the closed circuit formed by deep structures in the brain and the cerebral cortex (globus pallidus-ventrolateral nucleus of the thalamus, motor cortex-globus pallidus) is determined by the higher frequency of signals arriving in this closed circuit from the external thalamic center which, as is well known, plays an important role in the generation of EEG rhythms. The result of this is that oscillations of frequency equal to exactly half the frequency of the external action become established in the circuit, and the amplitude of these oscillations shows a rapid increase.

c. On the possible role of multiperiodic EEG patterns in the "writing" and "reading" of long-term memory traces

The facts and ideas presented above touch upon at least two more general points. Firstly, to a considerable extent, these results confirm the heuristic nature of the proposed scheme for the interaction between the cerebral cortex and thalamic oscillators during the evolution of EEG rhythms. Secondly, and no less importantly, they may be treated as evidence in favor of the fundamental assumption of functional significance of these rhythms, since interruption of such rhythms is accompanied by a clear interruption of cerebral functions.

It was natural to try and analyze, in the light of the above model ideas, the question of the possible functional significance of EEG rhythms, and to formulate at least a partial hypothesis that would not be inconsistent with the main body of experimental data whilst retaining internal unity and enabling us to exploit more fully the modern theory of nonlinear oscillations.

The ability of thalamic oscillators to generate an enormous (practically infinite) set of multiperiodic patterns, represented by the EEG rhythms and propagating over extensive brain territories, which follows from the properties of the evolution of "strange attractors," is particularly important for our proposed hypothesis. We propose that at least one of the functions of the EEG rhythms is to make a connection between the mechanisms responsible for them and the processes of retention of acquired experience, i.e., memory.

Our discussion will be confined to the mechanism of "writing" onto the brain substrate and "reading" of long-term memory traces. We shall not consider all

the preceding ("preparatory") processes, such as the reception of information, the existence of traces in short-term memory (measured by seconds, minutes, or hours), their selection for long-term memorization, classification, and coding (see Ref. 64). Nor shall we be concerned with processes occurring at the cell level and determining the substrate of imprinted traces. The hypothesis addresses itself to physiological mechanisms in the brain as a whole that are responsible for certain essential features of the formation and utilization of traces of events stored in the brain for long periods of time, probably, for the entire life of the subject.[7)]

The neurophysiological foundation for this hypothesis can be found in the numerous data indicating the plural character of the processing of specific information and especially memory traces in the brain, as well as data on special space-time patterns of neuronal activity that arise when the corresponding memory is used. These data were largely obtained in two types of experiment, namely, 1) experiments in which different portions of the brain were destroyed and a study was made of the retention of previously acquired knowledge or skills, ranging from simple conditioned reflexes[8)] to quite complex differentiated behavior, and 2) experiments involving the study of electrical functions in the brain in the course of processing and utilization of such knowledge. We shall now examine the basic results obtained in these studies.

Lashley and, subsequently, Sperry and other authors[12,65,67] used different experimental animals (ranging from the rat to the monkey) to demonstrate the surprising "tenacity" of retained skill after the removal of different portions of the brain, mainly areas of the cerebral cortex, and after the conductors connecting different cortical zones were cut. The removal of extensive zones of associative cortex and numerous scissions of connections between neighboring portions of the cortex by cutting it into small squares did not have any effect on formed habit. However, it is important in this connection that a certain critical amount of brain tissue be retained and the corresponding cortical inputs not be destroyed altogether. For example, it was found that, to ensure that the rat would retain simple visual differentiating habit (indicated by definite motion), that would be resistant to the removal of different associative or even motor zones of the cerebral cortex, it was necessary to retain at least 1/60 of the occipital cortex (the zone of visual cortical input), but it was immaterial which particular part was removed. Retention of complex habit depended on the total volume of removed cortical material; the removal of 50% or more independently of location led to the disappearance of the habit.

These facts enabled Lashley to formulate the proposition that memory involves the entire cerebral hemispheres, that it is everywhere, that each element (neuron) participates in the retention of many traces, and that the realization of a habit (utilization of memory) is mediated by a definite pattern of interacting neurons that can be activated from different brain sources.

Subsequent experiments using successive multiple ablations of the animal brain provided evidence for still further distribution of brain functions, including memory. Thus, when both occipital lobes of an animal were removed (from both hemispheres), i.e., the cortical inputs for visual information were removed, the animal became blind and was always deprived of the possibility of behavior corresponding to visual stimulus. When this ablation of the brain was performed in two stages, so that the occipital lobe was removed from one hemisphere and then, after an interval of a few months, the other lobe was removed, the final result could be different. When the animal actively used visual information to perform learned tasks in the interval between operations, and this information arrived through inputs in the undamaged hemisphere, then subsequent removal of the remaining visual cortex did not deprive the animal of the possibility of performance based on visual discrimination[68] (see also Ref. 12). Similar data were obtained in respect of bodily sensitivity.[69]

These data suggest the possibility of a plural representation not only of traces but also of sensory inputs at the cortical level, or even at the level of subcortical formations, and the decisive role played by active behavior during the reestablishment of function after repeated and temporarily separated brain traumas.

The results of experiments performed on animals and the general propositions based upon them were basically confirmed in respect of sensory discrimination in man. Thus, brain tumors producing damage to sensory projection zones (for example, the cortical input of bodily sensitivity—the postcentral gyrus), which can be accurately defined during an operation or in the course of post-mortem anatomical investigation, are often accompanied by the absence of a definite correlation between the localization of the tumor and the degree of damage to sensory discrimination. When the tumor destroys the postcentral gyrus, there is very little loss of discrimination within the framework of bodily sensitivity, and in half of all cases, no damage is observed at all.[70,71] Neurophysiological studies by the EP method have shown that, firstly, the application of a bodily stimulus produces responses recorded in the cortex well outside the limits of the damaged projection zone and, secondly, the degree of loss of function is closely correlated with the volume of the brain tumor tissue and the corresponding extent of neurodynamic shifts determined by the zone of disappearance or major distortion of the EP.

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7) According to existing data, loss of memory is not due to the "erasure" of traces but to difficulties in "reading" these traces (i.e., finding the "address" in the store).

8) We recall that a conditioned reflex is formed as a result of a coincidence (usually repeated) in time of a previously indifferent (neutral) stimulus and an activity essential for the animal, either congenital or acquired (eating, defense, and so on). As a result of learning, a previously neutral stimulus becomes a signal (conditioning or conditioned by previous coincidences) and evokes in the animal that type of action the connection with which became established as nonrandom and became fixed in memory.

A similar distribution of inputs is seen even at the level of thalamic relay nuclei. It is known that patients suffering from Parkinsonism and subjected to bilateral ablation (for therapeutic purposes) of thalamic nuclei through which certain types of bodily sensitivity (sensation of touch, pressure on skin, displacement of portions of the body) are switched over along the pathways to cortical projection zone, will either lose the sensory defect after a few months following the brain operation, or the defect will take the form of minor quantitative deviation without any selectivity with respect to some particular part of the body.

Since dead nervous tissue cannot be reconstituted (neurons are among cells that do not multiply after the completion of the embryonal development of the central nervous system), it is obvious that existing nerve networks undergo a well-known functional reorganization and acquire the ability to exploit information stored in the brain in a distributed form. Moreover, the "reading" of this information can be initiated not necessarily through "classical" sensory inputs.

These facts have enabled many researchers to speak of the "holographic principle" of the distribution and storage of information in the brain.[67,72] They had in mind, in the first instance, the distributed nature of these processes and states, and their essential unity that is manifested in the case of injury to the brain in the change primarily in quantitative indicators of function rather than in qualitative or topographic indicators.

Electrophysiological studies have led to other, no less important and illuminating, results. In animal experiments in which single neuron activity was recorded (through inserted microelectrodes), it was established (see Ref. 73 and the review published in Ref. 12) that: a) most brain neurons generate continuous pulse activity even under conditions of relative rest, which obviously reflects continuing information processing within the brain, and b) each cell *eventually* exhibits significant changes in its discharges as a result of repeated application of an arbitrarily chosen stimulus. These data were confirmed by many authors in situations involving simple learning (generation of a simple conditioned reflex), using both activity indicators of individual neurons and neuronal populations, in particular, by using EP recordings (see the review published in Ref. 12). It was shown that the characteristic changes in neuronal activity are observed not only practically universally in the cerebral cortex, but also in formations in the limbic system, i.e., subcortical (including thalamic) nuclei and the reticular formation of the brainstem. Although it is difficult and, sometimes, indeed, impossible to determine which particular neuronal activity is connected with direct processing of special information and which with the "servicing" of this processing (processes of attention, motivation, intention, evaluation of significance, preparation to respond, preparation for motion, emotional reactions), these data undoubtedly indicate that practically the entire brain is involved in any particular activity.[74]

Very important data on the plural nature (distribution) of long-term memory traces in the brain were obtained as a result of systematic studies by John *et al.*[12,75-78] It was established that the learning process in cat was accompanied by characteristic changes in the activity of neuronal populations, produced by a conditioning stimulus (for example, flashes of light), which take place over extensive brain territories located well beyond the limits of the specific projection system (in the present example, the visual system). When the averaged EPs were examined, these changes were found to be reflected to their late components that appear 50–2000 ms after the application of the conditioning stimulus and determine the characteristic pattern of the EP. When stimuli of the same sensory modality (visual by flashes of light or auditory by clicks) are applied in two situations with different frequency and produce different behavioral learning (memorization), the shape of the late EP components is different. When these tasks are firmly learned, the unexpected presentation of the same stimuli at a new (intermediate) frequency produces in the animal a response reaction that corresponds first to one or then to other learned task (depending, evidently, on the animals evaluation of which of the original stimuli is closer to the new stimuli). It is found that, under these conditions, the EP waveform corresponds not to the actually presented stimuli of new frequency, but to the stimuli of that frequency to which reproduced response reaction corresponded (compare with Fig. 17). Once again, these changes in the EPs were recorded over extensive brain territories.

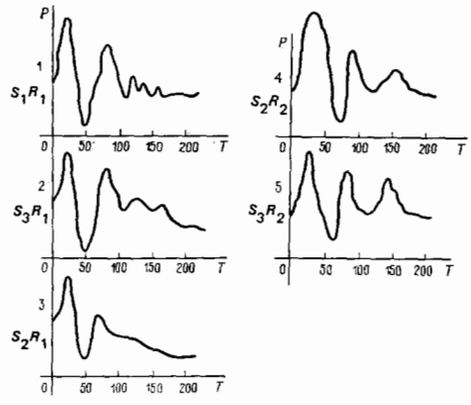

FIG. 17. Schematic illustration of different conditioned responses to light stimuli of two different frequencies, followed by a stimulus of intermediate frequency. It is clear that the character of the time distribution of the resultant activity of the neuronal population (PSH envelope—see text) depends not on the parameters of the conditioned stimulus but on the form of response reaction of the animal. 1—conditioned stimulus of particular frequency (S_1) evokes the corresponding reaction (R_1), 2—stimulus of intermediate frequency (S_3) evokes the same reaction, 3—the same reaction is produced erroneously in response to another frequency (S_2) used previously to evoke another conditioned reflex, 4—presentation of this stimulus evokes a different corresponding reaction (R_2), 5—the same reaction appears in response to the intermediate frequency stimulus. This scheme represents the results in Ref. 78. Horizontal axis defined under Fig. 18.

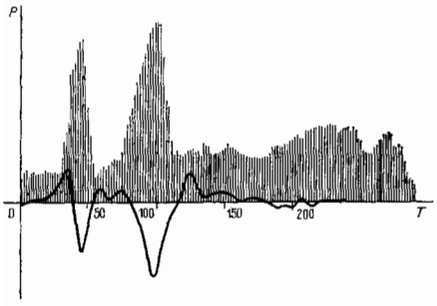

FIG. 18. Schematic illustration of the connection between visual EP components (solid line) and the dynamics of discharges of pulses by the neuronal population as seen on the PSH (thin vertical lines). Recorded in the same part of the brain. Summation of a series of responses to conditioned stimulus after a conditioned reflex in cat (based on Ref. 77). Horizontal axis—time T in ms, vertical axis—probability P of discharge impulses.

Basically the same results were obtained in an evaluation of the activity of neuronal populations in which simultaneous recordings were made of the impulse activity of groups of neurons in many zones of the brain with accumulation of results under repeated presentation of stimuli, using the method of post-stimulus histograms (PSH). These histograms reflect the probability of appearance of impulses resulting from neuron discharges at definite intervals of time after the presentation of the conditioning stimulus, and were in reasonable correspondence with the EP components (the pattern is shown in Fig. 18). It was shown that the behavior of a particular neuron in a given population is not rigidly fixed. The number of contributions necessary to reveal the characteristic pattern on the PSH is found to depend on the number of neurons whose activity has been recorded simultaneously: when the latter number was large, a smaller number of repeated measurements was necessary and, conversely, when the number of neurons was small, a proportionally higher number of repeated measurements was necessary. In other words, the coupling of a particular neuron with a particular action, and a specific component of the EP recorded in the same brain zone, is probabilistic in character.

Thus, both indicators of neuronal activity (EP and PSH) were found to contain a component that was clearly connected not with the presented stimulus, but with a previously learned habit, i.e., a process reflecting the realization of memory. John has referred to this as the "readout" component.

The following basic conclusions can be drawn in summary of the above experimental results:

1. A plural representation of information processing related to the performance of particular action is present in the brain. It is reflected, in particular, in the distributed nature of long-term memory traces, the plural nature of sensory inputs (with multiplication of the specific sensory stream, possibly, in projection, or the so-called associative, thalamic nuclei[9]), and in the retention or rapid restoration of brain function after quite extensive brain damage.

2. Trace changes are reflected in the activity of neuronal populations recorded on extensive brain territories in the form of characteristic changes in relatively late components of EP and PSH patterns whose origin is related to spontaneous EEG rhythm mechanisms.

3. Trace changes reflected in the "readout" components of EP and PSH are found to be coupled not so much to physical (sensory) properties of received signals as to the character of the action connected with them. This fact, and the connection between trace changes and late EP components, suggest action-directed perception of objects in the external world, perception that is "turned on for action,"[25,79] including sensory action (cognition), and its imaging in this form in memory traces.

Electrophysiological studies performed on human subjects are in good agreement with the foregoing conclusions. It has been shown that the evoked potential appears in response to stimuli of any modality in practically all parts of the hemispheres, and that there is a connection between the late component and internal operations performed on the basis of past experience, including those connected with speech (Section 1c and Ref. 80).

This entire set of data lies at the basis of ideas on the organization of memory in the brain that have been combined within the "theory of statistical configuration."[75] According to these ideas, long-term memorization of even a single event is represented by changes not in some restricted portions of the brain or connections between them, but by extensive brain territories (in the limit—the brain as a whole). A definite space-time configuration (a drawing or pattern) of neuronal activity, which can be referred to as the imaging ("representational") system appears on these territories under the influence of nerve impulses produced by a sequence of external stimuli that are nonrandomly related to the memorized event or action, and in connection with other processes in the brain itself (including associations related to past experience). It is proposed that it is precisely this stable configuration of ordered activity of the neuronal populations or ensembles (with a statistically determined participation of each population element) that is invariantly related to the stored information and can reproduce it. John emphasizes[75,76] that this theory is a consequence of the highly organized and differentiated structure of the brain, the dependence of the character of the imaging system on interactions between neurons within the ensemble, and the role of modifications that arise in the neurons themselves.

The "statistical configuration" theory overcomes at least two basic difficulties that are encountered in attempts to explain brain memory: it explains its distributed character (same patterns in different brain structures) and the ability of the same neuronal population to participate in the memorization of many

[9] This is a modification of the scheme described in Chap. 1, d.

characteristic features or events by organizing different space-time patterns. This provides a justification for Lashley's proposition, cited above, namely, that memory is everywhere in the brain and that each of its elements is a carrier of many traces.

However, the published papers do not provide an answer to a question that is crucial to the entire theory. This question relates to the nature of the brain mechanisms responsible for the formation of the large number of specific space-time patterns of neuronal activity that provides a particular pattern for practically each remembered event, and the question of the possible memory readout mechanism. However, as soon as the EEG waves appear as a result of a functionally significant nonlinear interaction of thalamic oscillators working in different frequency ranges, which results in the generation of multiperiodic and stochastic states, it is possible to put forward a hypothesis about the nature of this mechanism. From the standpoint of neurophysiology, this hypothesis is based on a new interpretation of the data presented in Section 2 on the bifurcation at the level of the brainstem and its higher portions of the stream of impulses into "specific" and "nonspecific" streams. If, as before, the former is looked upon as connected with the transmission and processing in special sensory systems of the brain of the information about an event that is encoded in the sequence of nerve impulses, then the functional significance of the second ("nonspecific") stream passing through the reticular formation must be evaluated in a new way. It is suggested that it implements the transmission of impulse volleys bearing sensory and other specialized information that arrives at different portions of the brain ("specific" and "nonspecific") as individual perturbations of the system of thalamic oscillators, thus modifying their interaction and resulting in the generation of a new multiperiodic EEG pattern. These rhythmic patterns emerge on extensive brain territories (in accordance with the diffuse nature of projections of thalamic oscillators onto the higher portions of the brain) and again interact with the "specific" stream of impulses (which is distributed through the multitude of sensory inputs) on the imaging (memorizing) neuronal systems. The secondary convergence of the two streams is, in fact, responsible for the changes in the neuronal substrate that represent long-term memory traces.

The presence of this convergence is revealed by analyses of the interrelation between the early part of the EP, the late part of the EP, and the afterdischarge. We have already noted (Section 1c) published data[16,17] demonstrating the duplication of early EP components by late components. It has also been shown that there is a correlation between the EP and its afterdischarge. The characteristics of the afterdischarge are, in turn, closely related to the individual characteristics of the "spontaneous" EEG of a given individual.[18] Neurophysiological studies performed on human subjects thus enable us to formulate the following firm propositions:

a) there is a close connection between the stimulated and spontaneous electrical activity of the brain

b) it is possible to isolate in both spontaneous and stimulated EEG a number of electrical phenomena connected with the inflow of impulses through the specific and nonspecific afferentation systems, and the two streams of pulses are found to interfere; this interference is most clearly seen in the region of late EP components and the afterdischarge

c) there is a definite connection between the specific characteristics of the stimulus and the reaction to it, and the specific pattern of electrical potentials that appears when the stimulus is presented and the corresponding reaction takes place.

This hypothesis provides a good explanation of how an enormous number of necessary patterns of neuronal activity can arise in the brain during the memorization of different events, and also their distributiveness within the brain. It explains, as already noted, the short duration of these patterns in real life which involves constantly varying actions and impressions that require the utilization of memory and the fixation within it of new experience. In a state of active wakefulness, these patterns follow one another on the EEG practically continuously, and can probably be revealed only by the method of averaged evoked potentials. Late components of the latter may be thought to reflect the individual multiperiodic pattern that characterizes, according to published data,[12,75-78,80] the remembered event. This is supported by the above information (and that given in Section 1c) on the participation of mechanisms responsible for the spontaneous EEG rhythm (thalamic oscillators) in the evolution of late EP components. Their duration (of the order of a few hundred milliseconds, i.e., including a few waves in the frequency range corresponding to the normal EEG in the state of wakefulness) is sufficient to reveal the specificity of the pattern. In view of the foregoing data on the correlation of the pattern which not so much physical characteristics of the stimulus as the action connected with it, we are led to propose that, in addition to the "branching" of the stream of impulses propagating along the sensory projection system, there is also a substantial (if not decisive) contribution of other brain structures to the nonspecific stream of impulses propagating over the reticular formation to the thalamic oscillators; these structures are related to different levels of brain hierarchy (including higher levels) and play different roles in the evolution of action (motor, sensory, and mental). It may be assumed that this contribution is largely connected with the realization of "internal" appraisal of remembered events. Finally, the fact that the interaction of thalamic oscillators that is connected not only with a change in the "nonspecific" influx along the RF, but also with the preceding interaction between these oscillators, is reflected in the nature of the multiperiodic pattern, can be brought in to explain memory dating processes, i.e., the inclusion in memory of the entire complex of spatial and temporal characteristics of a situation—its history.

Research into the stochastization of the oscillations of dynamic systems[3-5] enables us to say that memori-

zation includes the functionally essential process of stochastic modulation. This assures a degree of accuracy and protection from interference that would be unthinkable in determined addressable systems, the uniform utilization of the memorizing substrate, the possibility of redistribution in case of damage, and the striking flexibility of the operation of the brain that does not admit of a deterministic description. The encoding of information by a random signal is a widely known technical device ensuring maximum possible protection of a single communication channel from interference. If, at the same time, provision is made for enormous duplication of channels and receivers, the nature of the operation of the system may turn out to be qualitatively different. Thus, the reading and demodulation mechanism may become relatively economic as soon as the recorded trace can be activated again by the action of only the one component necessary for memorization, namely, the wave pattern that has a definite statistical relationship with the memorization pattern. The writing and reading patterns need not necessarily be identical. In this sense, recall or recognition is the reissuing of information that has been stored for a long period of time.

We are thus in a position to formulate some general ideas on the probable conditions and the sequence of events in neurons of the mirroring system when a trace is written and read. Apparently at least two conditions must prevail for writing: 1) convergence on a neuron of "specific" impulsation and the required wave pattern or, more likely, its phase, and 2) the neuron must not be "busy" at this time. The combination of the hypothetic "not-busy" and "respond" factors provides an explanation of such properties of long-term memory as only the probabilistic statistically expressed, rather than rigidly fixed participation of a specific neuron in different cases of activation of a given mirroring system (with the appearance of the characteristic EP and PSH pattern), and the increase in the possible number of potential "participants" in the system under repeated activation, which facilitates and makes more reliable the recall of memory ("repetition is the mother of learning").

Within the framework of this hypothesis, we note a definite similarity between writing into and reading out from memory in the brain, on the one hand, and a hologram, on the other. In both cases, the memory is distributed and is provided by the interaction of two factors namely, the information itself about the event (its "image") and a certain wave "addition" (see also Ref. 81). However, this exhausts the similarity. There are sharp differences as compared with the hologram: the wave "addition" is not a coherent (or some other) radiation without sensible connection with the image, but a multiperiodic pattern, i.e., a particular manifestation of the spontaneous rhythmic activity of the brain, which is specifically related to the recorded event (phenomenon, action) and is determined by it.

Certain aspects of the hypothesis remain unclear and unproved. In particular, so far, there is no answer to the crucial question, namely, what is it that is memorized by the neuronal ensembles in the brain? Is it a direct reflection of a whole specific situation, or is it a text written in terms of a single alphabet whose elements are the result of primary learning at early stages in the life of the individual (and, possibly, of the species), with the aid of which each remembered event is written only in the form of "addenda" to preexisting texts and recombinations of the latter, so that repeated recording of what is already contained in memory is avoided (in accordance with the "cassette metaphor" of Arbib[79])? There are also questions that are more directly related to the hypothesis and referring to both the substrate and the "mechanism" level of discussion. Direct experimental verification of the basic assumption is the central question: is it a fact that trace changes occur in the brain neurons under the influence of impulse characteristics of an event and of a specific pattern, which can subsequently be selectively activated only by a multiperiodic pattern? Other questions that must be analyzed are: what is the contribution of the natural oscillatory properties of the cortex to this process; what is the role of the natural frequencies of thalamic oscillators (which, as we know, are subject to considerable variation) in determining the characteristics of a multiperiodic pattern that is the result of their interactions; and just how is the required pattern activated in recall?

As far as the last question is concerned, it is obvious that, even when the rate of direct sampling is high, this type of mechanism can hardly be adopted. In principle, multiperiodic patterns can be as specific and as individual as the unrepeatable individual events in real life. However, apart from individuality and unrepeatability, events have common elements as well. If these common elements affect the evolution of the multiperiodic EEG patterns, we have a basis for a classification and, consequently, for restricting the sampling zone. The common elements may be contained not only in external events but also (and, in all probability, to a considerable extent) in internal states: motivations, emotions, attitudes, and character of wakefulness, which may result in a different contribution of thalamic oscillators operating in different frequency ranges to the overall generated pattern, and may also be the basis for an internal classification. In view of the foregoing, it may be considered that the pattern that performs the reading operation can, to some extent, differ from the pattern that has participated in the writing of the trace.

Another problem to be resolved is the connection between the generation of the multiperiodic patterns in the cerebral hemispheres and their functional specialization (Section 1d).

It seems to us that our hypothesis has definite advantages. Firstly, it is not inconsistent with any of the facts known to us, and has no internal inconsistencies. Secondly, it provides us, if only partially, with a functional interpretation of spontaneous EEG rhythms, and points to one of the possibilities of their participation in mechanisms responsible for the overall activity of the brain (we do not at all maintain that their purpose is exhausted by this function). And, finally, and par-

ticularly importantly, it points us in a specific direction for further researches in the light of both the necessity for, and fundamental possibility of, experimental verification.

CONCLUSIONS

1. The basic theme of this paper has been the attempt to illuminate certain possibilities of the physical approach to the explanation of particular phenomena observed in the brain of man and the higher animals.

Modern theory of nonlinear oscillations enables us to look upon multiperiodic and even stochastic processes as the result of an interaction between a few (or many) relatively simple dynamic systems that are not exposed to random external perturbations (noise and fluctuations). This enables us to absorb in our analysis biological oscillatory systems, the normal operation of which involves such states as quasiharmonic, beats, multiperiodic, and near-stochastic states.

The most interesting systems of this kind include the system of interaction of major portions of the brain, and the interaction between neuronal ensembles within such portions. The result of this is the appearance of slow oscillations in the potentials in brain structures. The frequency range of such oscillatory processes is 1–35 Hz. They are observed on the surface of the head, or directly in various zones of the cerebral cortex, in the form of the background electroencephalogram and evoked potentials.

2. We have given a review of the present state of knowledge concerning the structure and activity of the brain in sufficient detail for our purpose. The system of interactions between many brain structures (thalamus, reticular formation, brain stem, neocortex, limbic system), which form the so-called "nonspecific" pathway for information processing, is of particular significance for oscillations in the potential that constitute the EEG rhythms. When the dynamic properties of this system are examined, the basic concept is the above interaction of oscillatory processes in the cortex and the thalamic nuclei, which have, respectively, the properties of a nonlinear, passive oscillatory system with damping (cortex, according to Burns) and the properties of autogenerators (certain thalamic nuclei, according to Andersen *et al.*).

3. Within the framework of these ideas, it is possible to perform an analytic examination that enables us to explain the mechanisms involved in the generation of normal EEG rhythms and those responsible for certain pathologies in brain activity. This makes use of the Wilson-Cowan model of neuronal activity. By introducing certain definite modifications into the Wilson-Cowan equations, we can find an approximate analytic solution for problems relating to the operation of the thalamic autogenerators, and then determine the frequency of these oscillations and establish the conditions for frequency division when the thalamus acts on the oscillatory elements in the cortex. Analytic solutions obtained in this way provide us with a ready and graphic means of evaluating the significance of different parameters in the equations and their influence on the evolution of particular processes.

Frequency division with simultaneous increase in the amplitude of oscillations is a characteristic feature of paroxysmal rhythms recorded in EEGs during generalized epileptic seizures of all types (petit mal, grand mal, psychomotor automatism). These phenomena have long been known in physics and radio-engineering, and constitute nonlinear parametric excitation under conditions approaching parametric resonance.

Similar phenomena occur in the tremor observed in patients suffering from Parkinson's disease. This disease clearly exhibits features characteristic of parametric resonance: frequency division and increase in oscillation amplitude.

4. In contrast to model studies using hypothetic nervous tissue, which lead to arbitrary states, we have considered the interactions between real brain structures. The discrete frequency spectrum of the thalamic autogenerators is realized in the cortex in the form of the EEG rhythms.

We have examined certain features of the EEG and changes in these features in the course of normal brain activity in states of wakefulness and sleep, and also anomalous shifts. We have demonstrated their connection with changes in the interaction between thalamic autogenerators and with the degree of synchronization under the influence of different perturbations arriving in the final analysis through the reticular formation. We have made an attempt to explain the functional significance of the division of the stream of information in the higher branches of the brain into "specific" and "nonspecific," and the subsequent convergence of the two streams (after the transformation of the "nonspecific" stream into thalamic rhythms) in the elements of the cortex.

5. Analysis of a simple model for the interaction between the autogenerators within the framework of our scheme enables us to consider that the interaction between the thalamic autogenerators, on the one hand, and the reticular formation, on the other, may lead to the generation of an enormous number of different oscillatory processes that act on the cortex and excite in it a space-time distribution of oscillatory potentials and neuronal action currents (wave and the corresponding impulse patterns). It seems to us that the generation of a practically unlimited set of such patterns that are statistically coupled to the information that is being processed reflects very important aspects of the functional organization of the human brain and that of the higher animals, and, in particular, is related to the inscribing and reading of long-term memory traces.

We have suggested that the inscription (fixation) of a long-term trace is brought about by the above-mentioned convergence on the recording substrate of two effects, namely, trains of impulses arriving along "specific" information pathways and the multiperiodic wave pattern connected with them, which appears as a result of a change in the interaction between thalamic autogenerators under the influence of the same impulse

trains transmitted by the reticular formation. It is also proposed that the mechanism of reading (recall) is the result of the activation of a fixed trace under the influence of a single component that had participated in writing, namely, a wave pattern of a particular structure, which can arise, without external disturbances, as a result of internal stimulation alone.

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