Modern Neurophysiological Research of the Human Brain in Clinic and Psychophysiology

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Abstract. The article presents a comparative classification of most of the known methods for studying the human brain in clinic and psychophysiology. The informativeness of methods for assessing the state of the brain by electric and magnetic dipoles, as well as by various parameters of blood flow, is discussed. In conclusion, a comparative table of the main methods of neuroimaging is given. The table is based on research levels and time – from milliseconds to several years. The most sensitive methods are EEG, ERPs, MEG, ECoG, the less sensitive ones are fMRI, USDG, NIRS, EDA. PET is even less sensitive. A number of methods exist for the study of nuclei, neurons, synapses and separate sections in biophysics and molecular biology.. Along with general methodological approaches, some historical aspects of the development of methods of clinical neurophysiology are highlighted.

Keywords: EEG · Evoked potentials · Brain computer interface · Electro-dermal activity · Near-infrared spectroscopy

1 Introduction

Neurosciences in the XXI century characterized by the simultaneous development of new technologies of surgical neurosurgical interventions and visualization systems (neuronavigation, neuromonitoring, mapping, etc.) of the brain state. Preoperative morphological diagnostics is carried out according to the data of magnetic resonance imaging (MRI), computed tomography, angiography and MRI angiography. Physiological support is provided by functional MRI, positron emission tomography (PET), magnetoencephalography, traditional electroencephalography (EEG), evoked potentials (EP). Doppler ultrasound (USDG), functional MRI, PET, functional stereotaxis (using the methods of dipole localization, neuronavigation and 3-dimensional Lissajous trajectory), neurovideoendoscopy allow recording the brain state in real time [8, 9, 12, 18].

2 Electroencephalography. Neurophysiological Basis

Electroencephalography is a method for brain research based on recording its electrical potentials. According to its intended purpose, the EEG can be divided into clinical and

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physiological. Clinical EEG is used to diagnose brain diseases. These are verification of electrical activity disorders, localization of injuries, prediction of outcomes of brain damage, etc. Physiological EEG allows one to reveal correlates of mental functions in the state of electrical activity of the brain. This makes it possible to reveal the regularities of the functioning of a healthy brain, and the results obtained can be used for professional selection, dynamic observation of the functional state of people during their professional activities [19].

The concept of statistical display of the activity of multiple neural potentials based on the total EEG data seems to be the most adequate at present. The concept suggests that EEG is the result of a complex summation of the electrical potentials of many neurons working independently. The bioelectrical activity of the brain reflects the gradual fluctuations of somatodendritic potentials corresponding to postsynaptic excitatory and inhibitory potentials.

The EEG in summary reflects the functional activity of huge populations of neurons. As a result, EEG is a process caused by the activity of a huge number of neural generators. The generated electric field appears to be heterogeneous throughout the brain and changing over time. In this regard, between two points above the brain or between points above the brain and distant from it, there are variable potential differences (dipoles), the registration of which is the subject of electroencephalography.

The priority in recording the electrical activity of the brain is shared by the England surgeon and physiologist Richard Caton (1842–1926) and the Russian physiologist Vasily Danilevsky (1852–1939). At 1875, independently of each other, Caton and Danilevsky have recorded the total bioelectric activity on the open brain of a dog in an acute experiment. Thus, 1875 can reasonably be considered one of the key points in the history of neurophysiology – the total electrical activity of the cortex was recorded in an animal with an open brain [3].

The creation of the electroencephalography method is closely related to the name of the Russian physiologist Vladimir Pravdich-Neminsky (1879–1952). In 1912–1913 he has completed and published articles in which he proved the possibility of recording the electrical activity of the brain from the surface of the head through the meninges, the bones of the skull and intact skin. In studies carried out in acute experiments on immobilized anesthetized dogs, Pravdich-Neminsky registers the electrical activity of the cerebral cortex from the intact scalp.

Thus, the date of birth of the experimental EEG can be safely recognized as 1912–1913, when the electrical activity of the brain in an animal was first recorded through the bones of the skull and intact skin.

Modern clinical EEG begins in 1929, when the German psychiatrist Hans Berger publishes an article “Uber das Elektroenzephalogramm des Menschen” [1]. Since the 1920s, Berger has been developing a method for recording the electrical activity of the human brain. For work, he independently designed an original device (“Berger’s EEG machine”). Berger identified two types of electrical activity – with a frequency of about 10 Hz, which he designated as the alpha rhythm, and with a higher frequency (beta rhythm). For the first time, the characterization of the alpha rhythm was given, which occurs when the eyes are closed, and when the eyes are opened or upon sensory stimulation, the alpha rhythm is replaced by beta activity. It was also reported that the

nature of the "brain waves" changes depending on the functional state of the brain, during sleep, under general anesthesia and hypoxia. It was shown that the nature of activity in a healthy person and in a patient with epilepsy is significantly different. Berger proposed not only the term "electroencephalogram" itself, but also the term "EEG".

The method of clinical EEG gained recognition only after the work of Berger was supported by the master of electrophysiology Lord Edgar Douglas Adrian – Nobel winner in Physiology or Medicine (1932), which he received together with Charles Sherrington for researching the functional activity of neurons. At a meeting of the Physiological Society in Cambridge in May 1934, Adrian and Matthews demonstrated with their demonstration the connection between the "Berger's rhythm", as they called the alpha rhythm, with the bioelectrical activity of the brain. The period from the second half of the 1930s to the early 1950s was marked by the rapid development of the EEG. The method was widely introduced into clinical practice. "Pioneers of electroencephalography": Gray Walter, Herbert Jasper and Wilder Penfield, spouses Frederick and Erna Gibbs, Nathaniel Kleitman – laid the foundations of classical neurophysiology [3, 10].

3 Brain Evoked Potentials

One of the techniques that are most successfully used in the study of perception processes is the method of recording the evoked potentials (EP) of the brain. Described for the first time by Richard Caton, above mentioned, in 1875, almost 50 years before the discovery of the EEG, the EP method now represents a "spatio-temporal window" of brain activity [19]. EP is the electrical response of the brain structure to a stimulus or to a certain event, a change in the internal or external situation. Therefore, in psychophysiological research, there is another name – event-related potentials (ERPs). As a rule, an oscillation in response to a certain event is recorded within a time interval of 300–400 ms.

EP registration is carried out in two ways: in response to single stimuli (single EP) and in response to a series of stimuli with simultaneous summation of evoked responses (averaged EP). In the latter case, the use of special computing devices is required, which extract a useful signal from the noise generated by spontaneous brain activity.

Before a wave self-oscillatory process, called EP, is formed, the registered dipoles must undergo a series of transformations in the biological amplifier. In addition to increasing the apparent amplitude of the signal, the amplifier performs the function of filtering (not removing artifacts and network noise) of the signal in a certain frequency range. So, for example, if the EEG is recorded in the bandwidth of frequencies from 0.5 to 30 Hz, then EPs require an expansion of the upper frequency up to 100 Hz for visual EPs and even up to 1000–2000 Hz for auditory (see Fig. 1) and somatosensory EPs during intraoperative monitoring in neurosurgery [9, 12].

The registered EP consists of a number of components reflecting the alternation of successive phases of polarization and depolarization of neuronal populations and the inclusion of an increasing number of brain structures in the analysis of the incoming signal. The time interval from the moment the signal is applied to the completion of the formation of the analyzed components is called the analysis epoch. Typically, studies requiring an assessment of the state of cognitive functions use an analysis epoch of 400 ms, although this can be extended to 1000 and 2000 ms [14]. Depending on the

stimulus used and, accordingly, on the objectives of the study, cerebral EPs are subdivided by modality into visual (VEP), auditory (AEP), and somatosensory (SEP). These three basic modalities have been adapted in both clinical and psychophysiological research.

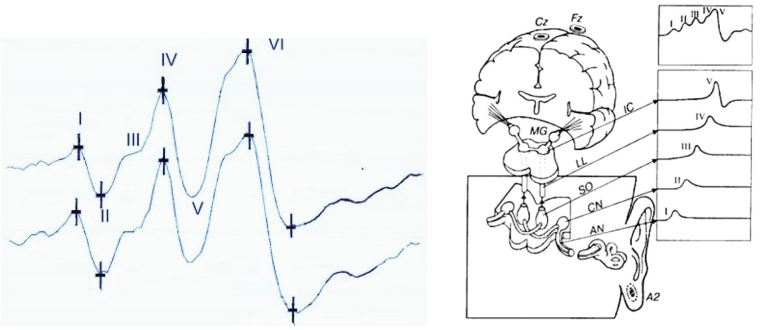

Fig. 1. The original short-latency auditory evoked potential registered during neurosurgery (left) and brain generators (right). AN – acoustical nerve, CN – cochlear nucleus, SO – top olive, LL – lateral lemniscuses, MG – medial geniculus. Epoch of analyze – 10 ms.

3.1 Evoked Potentials and Perception

The registered EP consists of a number of components reflecting the alternation of successive phases of polarization and depolarization of neuronal populations and the inclusion of an increasing number of brain structures in the analysis of the incoming signal. The time interval from the moment the signal is applied to the completion of the formation of the analyzed components is called the analysis epoch. Typically, studies requiring an assessment of the state of cognitive functions use an analysis epoch of 400 ms, although this can be extended to 1000 and 2000 ms [14]. Depending on the stimulus used and, accordingly, on the objectives of the study, cerebral EPs are subdivided by modality into visual (VEP), auditory (AEP), and somatosensory (SEP). These three basic modalities have been adapted in both clinical and psychophysiological research.

In terms of their physiological genesis, EP components are heterogeneous. Early waves (up to 70–100 ms) represent the primary response of nerve structures (nuclei of the brain stem, projection cortex) to the arrival of impulses along sensory pathways. Later components are associated with complex processes of intracerebral interaction, including the arrival of impulses from other parts of the cortex and subcortical structures, including nonspecific centers of the brain stem, centers of emotions and motivations. Between the early and late EP waves, there is a group of waves of mixed genesis due to sensory and non-sensory influences. In many psychophysiological studies carried out over the past 2–3 decades in various laboratories around the world, and during neurosurgical operations, the nature of the relationship between physiological and psychological indicators of perception had much in common. Early sensory EP waves (with PL up to 100 ms) show a high correlation with the indicator of sensory sensitivity, and the late ones, including the P300 wave, with the indicator of the decision criterion. Intermediate EP components

with a PL of 100–200 ms revealed a double correlation – both with the sensitivity index and the decision criterion [3].

Informative data on the essence of mental processes that make up the content of the third stage of perception were obtained in studies devoted to the analysis of the functional meaning and informational significance of the wave P300, which shows the highest correlation with the decision-making criterion. It should be said that over the past 40 years a phenomenon, and even a paradigm "P300" (see Fig. 2), has formed in the literature, combining not one positive oscillation with a peak latency of 300 ms, but a whole complex of waves following this period of time. The generalizing result of these works was the proposition that P300 reflects an important stage of cognitive processes associated with the recognition of a stimulus based on the comparison of available information with memory and the expectation formed on its basis [15].

3.2 Registration of Magnetic Fields

In addition to recording the electric component of the field generated around the head, systems for assessing the magnetic fields of the brain are being actively developed. It is believed that their possible sources are electrical currents arising in synapses and synchronously activating pyramidal neurons. The apical dendrites of these cells are located parallel to each other and perpendicular to the surface of the cortex, where primary intracranial currents are generated, forming an electric circle in the surrounding tissues. Consequently, the magnetoencephalogram (MEG) of a living brain is mainly a sensor of the activity of the fissural cortex.

The most interesting results were obtained in the study of magnetic EPs in response to auditory stimulation. It was found that the localization of the source of cortical auditory magnetic EPs moves with a change in the frequency of stimuli. This phenomenon is called the tonotopic organization of the auditory cortex. In order to localize the dipole of the pathological focus, according to the MRI data, the dimensions of the Hershel's gyrus (the primary projection zone of the auditory analyzer located in the temporal lobe) in different people were determined [6].

One of the essential features of MEG registration is the use of superconducting quantum interferometric device (SQUID). Such devices have the highest sensitivity among all existing magnetic flux detectors. Their principle of operation is based on the use of the magnetic flux quantization effect and the Josephson tunneling effect. Thus, the SQUID is a "magnetic flux-voltage" converter, which generates a voltage at the output that periodically changes depending on the applied magnetics flux with a period equal to one flux quantum. By analogy with bioelectric EPs, the registration of magnetic EPs in order to suppress the noise of SQUIDs and spontaneous MEG requires a large number of accumulations (tens and hundreds). To build brain maps, you need to use from 30 to 70 (up to 200) registration points.

The cost of devices for recording brain magnetic fields is tens of times higher than the cost of traditional EEG-EP.

3.3 Systems "Brain-Computer Interface" Based on P300

Last two decades practical studies of the P300 ERP component have been associated with brain-computer interface (BCI) systems, which, in addition to solving physiological and psychological problems, have medical and social significance. Modern BCI systems can use a number of electrophysiological signals – visual EPs, slow cortical potentials, alpha and beta EEG rhythm, and the P300 component of evoked potentials [16]. In Fig. 2 shows the original visual event-related potential during perception of oddball visual image. The red circle marks the late components that make up the P300 paradigm.

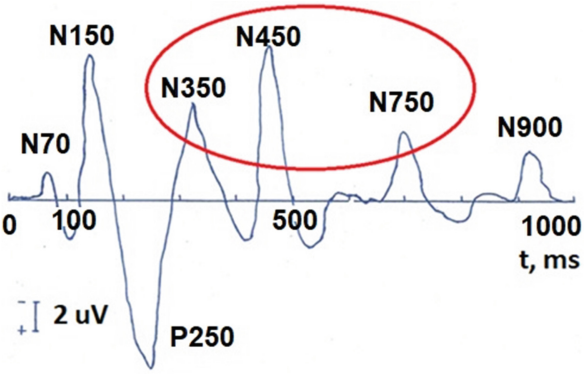

Fig. 2. Visual evoked potential (numbers – time, ms) according to the 10–20 system during the perception of visual image (oddball). Analysis time – 1000 ms.

In the BCI system, the digitized bioelectric signal recorded from the scalp is sent to the processing level, where the necessary features are extracted by applying spatial filtering and spectral analysis [23]. To extract useful information BCI can use temporal parameters of the signal (peak latency of the EP, P300 components), frequency characteristics of the EEG rhythms, spatial parameters, as well as a combination of all of the above characteristics [4].

The P300 wave attracted a lot of attention in BCI studies [7, 20]. Since the P300 only elicits oddball (strange) stimuli that require special attention from the user, it can be used as control signals in the BCI to select the desired choice. Users (subjects) can influence the amplitude of the P300, paying more attention to a specific event. Therefore, the P300 is used in many BCI systems to reveal intentions or information hidden in the EEG [16].

Persons with disabilities can use the P300-based BCI for communication [21]. The P300 spelling system (speller) is proposed, which allows subjects to transmit a sequence of letters to a computer. To create a "weird" oddball paradigm, a 6x6 matrix containing letters of the alphabet and numbers is displayed on the computer screen. A person can choose a specific sign by focusing attention on it. The BCI can also be used to drive a wheelchair. With the P300 BCI system, the user can select a destination in the menu by counting the number of flashes of the destination. Further, the wheelchair moves to the selected and desired destination along a predetermined path [16].

In addition to the wheelchair, an important application for people with severe motor impairments is the control of neuroprosthetic devices. BCIs can be used to control limb movements, for example, a robotic arm. It has been shown that BCIs based on the activity of cortical neurons are able to control three-dimensional movements of a robot arm [13].

BCI systems can communicate in paralyzed patients suffering from neurological or neuromuscular diseases (eg, amyotrophic lateral sclerosis (ALS). As the disease progresses, various conditions can be distinguished. In a completely blocked state, voluntary muscle control is lost. Many ALS patients achieve this conditions, have visual impairments and may not be able to use BCIs through the visual sensory system. Usually in these patients the auditory system is not damaged, therefore, studying the possibility of using BCIs based on auditory signals may be of great importance [23].

In the future, P300-based BCI systems are being considered for controlling combat information posts and computer virtual games.

4 Electrodermal Reactions. Super-Slow Physiological Processes

Electrodermal activity (EDA) is a set of bioelectric phenomena recorded from the skin surface. The potential level, conductivity and resistance of the skin reflect the state of the autonomic nervous system and are widely used in psychophysiology to assess the emotional sphere, neuropsychic tension, selective attention, etc.

E. Dubois-Reymond was the first to describe the potentials of the skin in 1848. He showed that the biocurrents of the isolated frog skin are superior in magnitude to the nervous and muscular ones [5].

Carl Jung (1907) showed the connection between galvanic skin response (GSR) and the degree of emotional experience. In GSR, Jung saw an objective physiological "window" into unconscious processes postulated by his teacher Sigmund Freud. Thus, from the beginning of the twentieth century GSR has become one of the most common indicators. This was due to the ease of its registration and the seeming simplicity of the interpretation of measurements. It has been widely and relatively successfully used to control the state of a person when performing various types of activities, in the research of the emotional-volitional sphere and intellectual activity. Galvanic skin response is one of the main indicators in "lie detectors".

Sweat glands are the source of EDA generation. Simultaneous recording of EDA from the skin and the secretion of sweat by a single sweat gland revealed that sweat secretion coincides with the deviation of the skin potential in the negative direction, and the latter, in turn, coincides with a decrease in skin resistance in response to a stimulus [2].

Although acetylcholine is the neurotransmitter for sweat glands, they are under the control of the sympathetic nervous system (for example, destruction of the sympathetic nervous system on one side of the body leads to the destruction of EDA only on that side). The sweat glands receive influences from the cortex and deep structures of the brain – the hypothalamus and the reticular formation. EDA is a suprasegmentally somato-vegetative reflex, the effector organ of which is the sweat glands, and the "generator" of the response is the posterior hypothalamus.

Super-slow physiological processes (SSPP) are in the same frequency range (less than 1 Hz) with the EDA. The study of the SSPP dynamics showed that they reflect the

level of stable functioning and are a physiological indicator that determines the state of brain structures and the course of a number of other bioelectric processes. To date, numerous studies have shown that SSPPs are an adequate physiological method for studying the cerebral system for providing emotions and mental activity.

So the EDA evaluates skin resistance, which is determined by the state of the sweat glands. Sweating, in turn, depends on the state of the autonomic nervous system. The study of the dynamics of skin resistance is used in devices called "lie detector". A person, answering the questions posed in monosyllables, is already in a state of heightened emotional stress. Control over the autonomic nervous system by the higher parts of the central nervous system is practically absent, which is reflected in the dynamics of the EDA with correct and incorrect answers. It should be said that a real boom in research using the "lie detector" was observed in the 50s and 70s of the 20th century in the practice of professional selection. EDA registration has also found its application in the practice of psychophysiological correction – in biofeedback devices. EDA registration data (possibly other indicators – ECG, EEG, electromyogram, etc.) are displayed on a display that is visible to the subject [22]. Conditions that modulate positive emotions are created for the patient for a certain period of time. At the end of the action of positive stimulants, neutral conditions are created, where a person, according to the values of GSR, controls his state, trying to maintain at the level of positive emotions.

5 Other Methods in Clinical Neurophysiology and Applied Psychophysiology (USDG, PET-Scan, NIRs)

The above research methods have found wide application in clinical and diagnostic practice, and are also widely used in assessing human conditions in various conditions, especially when testing new technology and new conditions of activity.

Fundamentally new data on the role of subcortical formations in the provision of neurophysiological mechanisms of mental activity made it possible to obtain the method of implanted electrodes, which was used for therapeutic and diagnostic purposes in clinical practice in the 70s–80s. It has been established that in the activity of the subcortical formations of the brain, the interaction of analyzers and systems that provide programming of purposeful behavior is clearly observed. However, despite the use of both gold and platinum electrodes implanted into the brain structures, this method turned out to be unnecessarily invasive for humans and is currently practically not used.

Austrian physicist Christian Doppler (1803–1853) in 1842 formulated a principle that makes it possible to assess the direction and speed of movement of any object by changes in the echo signal reflected from it. If this object is stationary, then the echo signal reflected from it returns to the radiation source after a time T, which is directly proportional to the doubled path from the radiation source to the object (2L) and inversely proportional to the propagation speed of this type of radiation C ($T = 2L/C$). If the object moves at a certain speed, then the time after which the echo signal returns to the radiation source changes, which makes it possible to estimate the speed and direction of the object movement. In medicine, the use of ultrasound radiation is widespread to assess the speed and direction of movement of red blood cells in blood vessels. Almost a century and a

half later, in 1982, the method of transcranial ultrasound Doppler (USDG) was proposed, which evaluates blood flow in the great intracranial vessels of the brain.

When examining blood circulation by the USDG method, the Doppler signal frequency spectrum represents the range of the linear velocity of red blood cells in the measured volume and is displayed as a spectrogram in real time on a unidirectional or bidirectional frequency analyzer. The signal is evaluated using a fast Fourier transform, the maximum frequency is plotted along the vertical axis in cm/s or kHz, and the time is either continuously or in freeze frame mode horizontally. The method allows one to simultaneously measure the maximum linear (systolic) velocity, the minimum linear (diastolic) velocity, the average blood flow velocity and the pulsation index (the ratio of the difference between the systolic and diastolic linear blood flow velocity to the average velocity).

Changes in the parameters of cerebral blood flow allows in psychophysiological studies to quantitatively assess the degree of participation of certain parts of the brain in providing cognitive activity of varying degrees of intensity.

Positron emission tomography is one of the most modern, promising and powerful neuroimaging methods. According to a line of authors, it is called "functional neuroanatomy of the human brain." The first publications on PET date back to 1975–1979, but the main stream of work appeared in the 80s. The main purpose of PET-scan is to study the distribution in the living brain of various (more than 200) chemicals it utilizes in order to assess one or another of its functions. Among them are blood flow, pH, metabolism, molecular diffusion, protein synthesis, activity of membrane receptors, and a number of others. Amino acids, carboxylic acids, amines, sugars, steroids, metabolites, drugs, and their derivatives are used as injected substances. The principle of the method is registration of radioactive decay (positron emission) of short-lived (2–110 min) isotopes (C, N, O or F), combined with a substance-tracer. Based on the principles of computed tomography, a three-dimensional display of brain radioactivity is constructed, consisting of huge number (up to 230 thousand) discrete points. The sensitivity of PET is very high – it allows the detection of test substances in the brain in concentrations of up to several picomoles per gram [11].

Modern technologies for registration of near infrared light (Near Infra-Red Spectroscopy – NIRS) allow detecting changes in blood flow and metabolic activity of the brain (similar to functional MRI), since these physiological processes are associated with the scattering of light infrared light. NIRS technology evaluates the neural and vascular activity of brain structures. The technique is based on changes in light scattering arising in the dynamics of blood oxygen saturation and local activity of neurons. In this way, safe infrared light is transformed through the bones of the skull and adjacent tissues from the superficial layers of the brain. Then it is removed from the scalp using a fiber-optic cable, turning into an electrical signal and transforming into a brain map [17].

The positive aspects of NIRS technology are the ability to assess local hemodynamics associated with neural activity in real time, the absence of artifacts and the portability of devices. NIRS studies of parental recognition ability in 2–3 month old infants have been described. One of the limitations of this innovative technology is the low penetrating ability to deep brain structures. However, the developers consider this shortcoming temporary. The future in NIRS technologies lies in increasing the temporal resolution

and depth of signal detection. Recent research indicates that light infrared light is also dependent on ion currents and water in neurons and glia, which brings closer real-time measurement of brain activity. Thus, the study of mental processes using objective methods opens up broad prospects for understanding the mechanisms of the brain. In turn, when assessing the prospects for studying each of the methods, it is important to emphasize that the complex application of an adequate set of economically feasible techniques greatly increases the effectiveness of research.

<table>
<tr><td rowspan="2">Research in time</td><td colspan="5">Research level</td></tr>
<tr><td>Brain</td><td>Mapping</td><td>Layers/ Nuclei</td><td>Cells</td><td>Synapses</td></tr>
<tr><td>Milliseconds/ seconds</td><td colspan="2">EEG, ERPs, MEG, ECoG</td><td colspan="2">Neural activity</td><td rowspan="2">Biophysics</td></tr>
<tr><td>Seconds/ hours</td><td colspan="2">fMRI, USDG, NIRS, EDA</td><td colspan="2">Vascular video microscopy</td></tr>
<tr><td>Days</td><td colspan="2">PET-scan</td><td colspan="2" rowspan="2">Angiography</td><td rowspan="2">Molecular biology</td></tr>
<tr><td>Years</td><td colspan="2">CT, MRI</td></tr>
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Fig. 3. Diagnostic methods for brain mapping.

As a result, let us consider what place the approaches of clinical neurophysiology occupy among the methods of brain mapping (see Fig. 3). Research levels are divided from the whole brain to cells and synapses. Research in time may vary from milliseconds to several years. The main feature of clinical neurophysiology diagnostics is time. As a rule, these are fractions of a second (ERPs), seconds (EEG, MEG, ECoG), minutes (fMRI). Only positron emission tomography reflects the state of the brain over several days, which is associated with the life cycle of radioactive isotopes. The level of research corresponds to the whole brain, maps, microelectrode (neural activity) allow you to explore individual neurons and nerve centers – nuclei.

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