# DIAGNOSIS OF EPILEPSY: FROM THE BEGINNING TO THE NEW HYBRID PET/MR TECHNIQUE

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## ABSTRACT

*The problem of diagnosis and treatment of epilepsy concerns medical society for a several thousands of years. The understanding of the causes and pathological mechanisms of this condition underwent numerous and substantial changes during this time, that allowed reaching significant advances in both the diagnosis or treatment. At the present time, there is a wide spectrum of diagnostic methods that allow localizing the epileptogenic focus, that is essential for planning the surgical treatment in patients with pharmacoresistant epilepsy. The results of the surgical treatment are strongly dependent on the diagnostic accuracy in the detection of one or several epileptogenic foci and on the prognosis of their resection. In this connection, the research on the possibilities and perfection of new diagnostic methods hold the potential to improve the results of the surgical treatment and the life quality in patients with pharmacoresistant epilepsy. This review presents a detailed description of the evolution of epilepsy diagnostics from the first implementation of electroencephalography in the 1920-s to the modern hybrid methods such as SISCOM (Subtraction Ictal SPECT Co-Registered to MRI) and PET-MRI.*

***Keywords:*** *epilepsy; diagnostics; magnetic resonance imaging; MRI; single-photon emission computed tomography; PET-CT; positron emission tomography combined with magnetic resonance imaging PET-MRI.*

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## INTRODUCTION

Epilepsy is a complex set of conditions ranging from asymptomatic to those accompanied by disability due to various types of epileptic seizures (convulsive and non-convulsive; focal and generalized), status epilepticus, and severe personality disorders [1].

Epilepsy has been known for thousands of years. In the past, it was referred to as a “sacred disease” and was believed to be caused by the gods visiting the patient’s body. Therefore, treatment was based on observing seizures [2]. The earliest known account of epilepsy was written by Hippocrates around 400 BC in his treatise “On the Sacred Disease” [3]. According to this account, epilepsy is caused by a brain disorder or injury and not by gods or spirits. Hippocrates referred to the fact that the sacred disease occurs in “watery” individuals (also called phlegmatic people). He believed that in epilepsy, liquefaction occurs in brain areas but never in “bile” individuals (jaundiced). If it were the will of the gods, it would occur equally in all.

The term “epilepsy” was first introduced by Avicenna in 1025 AD. The disease was defined as preventing the “mental organs” from functioning and preventing a person from standing in the brain’s attempts to expel something foreign. During the Holy Inquisition, the belief that epilepsy was of magical or diabolical origin was widespread, which hindered the search for effective treatments [2].

The nineteenth century marked the beginning of rapid development in epileptology. Before 1870, epileptic seizure was believed to originate in the medulla oblongata. However, the development of physiology led to the formation of the idea of the reflex arc. In 1833, Marshall Hall first described the structure of the reflex arc, and in 1836, he revealed that epilepsy develops because of pathology in afferent or central neurons [4]. Excitation, ascending along the arc from the afferent neuron to the medulla oblongata, causes laryngeal muscle spasm, leading to hypoxia and seizure development [5]. Furthermore, the role of the medulla oblongata in epilepsy development was noted by Brown-Sequard [6], Kussmaul and Tanner [7], van der Kolk [8], and Reynolds [9].

The idea that epilepsy originates in the cortex was initially proposed by Richard Bright in 1831. He



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# ДИАГНОСТИКА ЭПИЛЕПСИИ: ОТ ИСТОКОВ ДО ГИБРИДНОГО МЕТОДА ПЭТ/МРТ

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**АННОТАЦИЯ**

*Проблема диагностики и лечения эпилепсии интересует медицинское сообщество на протяжении нескольких тысяч лет. Представления о причинах и механизмах развития данного состояния в течение этого периода неоднократно претерпевали существенные изменения, что позволило достичь несомненных успехов как в диагностике заболевания, так и в его лечении. Широкий спектр диагностических методов на современном этапе позволяет локализовать эпилептогенный очаг, что имеет особое значение у пациентов с фармакорезистентной эпилепсией при планировании хирургического лечения. Результаты операции напрямую зависят от того, насколько точно удалось выявить эпилептические очаги (один или несколько) и оценить возможности их резекции. В этой связи исследования возможностей и совершенствование новых диагностических методик обладают потенциалом улучшения результатов хирургического лечения и качества жизни пациентов с фармакорезистентной эпилепсией. В статье подробно изложены этапы развития диагностики эпилепсии — от первого опыта применения электроэнцефалографии в 1920-х годах до современных гибридных методик, таких как SISCOM (Subtraction Ictal SPECT Co-Registered to MRI — субтракционная иктальная однофотонная эмиссионная компьютерная томография, совмещённая с магнитно-резонансной томографией) и позитронная эмиссионная томография, совмещённая с магнитно-резонансной томографией.*

***Ключевые слова:*** *эпилепсия; диагностика; магнитно-резонансная томография; МРТ; однофотонная эмиссионная компьютерная томография; ОФЭКТ; позитронная эмиссионная томография, совмещённая с компьютерной томографией; ПЭТ-КТ; позитронная эмиссионная томография, совмещённая с магнитно-резонансной томографией; ПЭТ-МРТ.*

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observed focal changes in the cortex of patients with convulsive seizures; however, his observations were not widely recognized at the time [5]. In 1878, Sam Wilks directly referred to the cortex of the large hemispheres. Wilks showed that the localization of changes and “local irritant syndrome” are crucial in the development of seizure syndrome and its specific manifestations, regardless of any changes found in pathological and anatomical examination of the brain [10]. John Dixon created the hypothesis of epileptogenesis based on Wilks’ work. Dixon defined an epileptic focus as an area of localized decrease in the energy activity of cortical neurons, resulting in decreased function control of this area. When a threshold value is reached, this area begins to reduce energy exchange in neighboring neurons, and the process spreads, causing vasospasm, which leads to epileptic seizures [11].

John Jackson is a pioneer of modern epileptology. In his 1870 article, Jackson has identified the cortical localization of the focus of seizure onset. Over the next two decades, he developed his concept which is now known as cortical epileptogenesis [12].

## MOLECULAR AND CELLULAR CHANGES IN EPILEPTIC FOCUS AND GLUCOSE METABOLISM

The mechanisms in epileptic foci formation have not yet been fully studied. However, epilepsy is

generally considered to be a result of canalopathy, which can be either genetically determined [13] or secondary, resulting from conditions such as stroke [14], tumor [15], and other diseases or metabolic disorders. There is a change in the ratio of inhibitory and excitatory regulatory impulses, resulting in a paroxysmal shift in depolarization. This shift is characterized by an increase in the resting potential of neuronal membranes in the epileptic focus, which increases their excitability. Epilepsy is characterized by a decrease in the efficiency of the mechanisms for the capture of $K^+$ ions by neurons during the development of the action potential. This leads to the maintenance and enhancement of the paroxysmal shift in the depolarization of neuronal membranes. It has been shown that epileptic foci are more likely to develop in initially more excitable structures in a healthy brain [17].

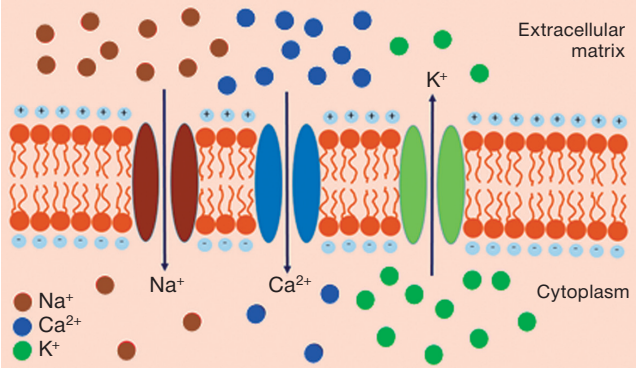


**Fig. 1.** Ionic currents during the action potential. The cytoplasmic concentration of $K^+$ ions significantly exceeds their extracellular concentration, in contrast to the concentration of $Na^+$ and $Ca^+$. During the propagation of the action potential, $Na^+$ and $Ca^+$ — channels and later $K^+$ channels are opening, that provides a concentration gradient for ions to flow.

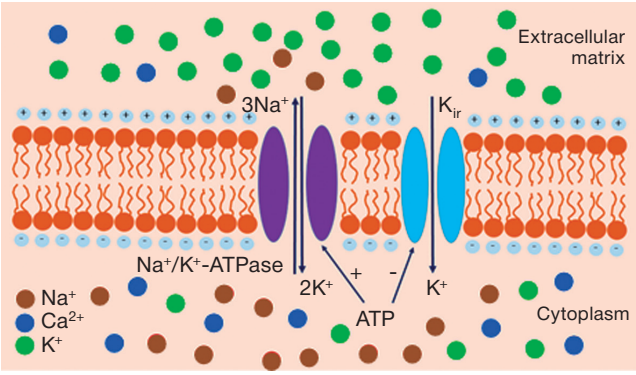


**Fig. 2.** Mechanism for the decrease of the $K^+$ ions' concentration in the extracellular matrix. The decrease of the $K^+$ ions' concentration in the extracellular matrix generally results from the effect of $3Na^+/2K^+$ adenosine triphosphatase and inward rectifying potassium channels $K_{ir}$. Functioning of adenosine triphosphatase requires the presence of adenosine triphosphate in the cytoplasm, whereas the increase of the adenosine triphosphate concentration leads to the decrease of the $K_{ir}$ channels' activity.

The action potential initiates when the threshold membrane potential is reached, and $Na^+$ and $Ca^{2+}$ ions enter the neuron, whereas $K^+$ ions exit. Restoring the resting membrane potential requires a decrease in potassium ion concentration in the intercellular matrix, which is mainly facilitated by $Na^+/K^+$-ATPase and $K_{ir}$ channels [18, 19]. The $Na^+/K^+$-ATPase enzyme hydrolyzes adenosine triphosphate (ATP). However, its activity is reduced in epilepsy, which may be a result of the mutation and a compensatory response to general pathophysiological changes [20, 21]. ATP concentration should decrease to increase $K_{ir}$-channel activity, which in turn decreases glucose demand. This may be a contributing factor to decreased $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) accumulation in the epileptic focus area during the interictal period, as visualized by positron emission tomography (PET). A possible explanation for the decreased $^{18}$F-FDG accumulation during the interictal period is a reduction in the activity of respiratory chain complexes in epileptic cells [22–24].

The propagation of an action potential in one neuron leads to its spread to all neurons in the pathological focus, resulting in hypersynchronization and spike activity on the electroencephalogram. Morphological studies of the resected foci tissues revealed a decrease in dendritic branching and excitatory synapse closure among neurons [25]. Inhibitory synapses increase over time, and hyperpolarization develops perifocal to the epileptic focus, hindering the propagation of paroxysmal impulses. During impulse development, inhibition occurs at the expense of the perifocal zone and a few inhibitory endings in the focus itself. This is registered on the electroencephalogram (EEG) as a slow wave whose size exceeds the size of the epileptic focus [25].

The development of an action potential in neurons releases neurotransmitters (Fig. 1 and 2). The most common excitation–inhibition system involves glutamate/gamma-aminobutyric acid mediators [26–28]. The effect of action potential development depends on whether it originates from an inhibitory or excitatory end. However, neurotransmitter release requires energy expenditure [2]. Thus, whether observing excitation or inhibition, PET imaging with $^{18}$F-FDG will visualize this process as a zone of hypermetabolism [29]. Additionally, after neurotransmitter release, a new


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portion should be synthesized. Vesicle transport to the synaptic end of the neuron takes several hours to several days [22], during which energy expenditure and glucose metabolism increase [30].

Inhibitory mediator gamma-aminobutyric acid (GABA) release leads to membrane hyperpolarization primarily through the opening of chloride channels. This prevents the propagation of the epileptic impulse [22]. GABA synthesis and exocytosis require active energy expenditure. Zones of active inhibition during PET studies in the ictal period are visualized as foci of $^{18}$F-FDG hypermetabolism [29]. Thus, the zone of pathophysiological changes includes the epileptic focus and perifocal zone, which prevents impulse propagation from the focus. PET studies have shown $^{18}$F-FDG hypermetabolism in both of these zones during the development of epileptic seizures. This is due to the active release of excitatory mediators in the focus and an attempt at compensatory inhibition and active exocytosis of GABA in the perifocal environment. Furthermore, comparable enhancements in metabolism can be observed in the opposite homotopic region and in other regions that are functionally linked to the focus through collaterals [28]. Simultaneously, constant background hyperpolarization in the perifocal zone may reduce the overall functional activity of the surrounding area. This results in decreased glucose consumption and the emergence of a hypometabolic area that encompasses both the focal and perifocal zones in PET studies using $^{18}$F-FDG during the interictal period [31].

Thus, at the cellular level, the main mechanisms of the decrease in $^{18}$F-FDG metabolism in the interictal period include reduced glucose uptake from the vascular bed in response to inhibitory effects in the perifocal zone and decreased active neurons due to depletion and death. However, hypermetabolism during the attack period and within 2 days after the attack is associated with a significant increase in glucose consumption due to the need for compensatory synthesis and transport of neurotransmitters. The size of the $^{18}$F-FDG hypometabolic zone in PET studies during the interictal period is often larger than the actual size of the focus. This can be explained by the inclusion of the perifocal inhibitory environment into the zone of pathomorphologic changes in addition to the epileptic focus. However, increasing the size of the resected area to match the hypometabolic area has not been correlated with improved surgical outcomes. Changes in the perifocal area are often reversible [34].

## DEVELOPMENT OF EPILEPSY TREATMENT TACTICS

The idea that a focal anomaly could cause seizures led to the proposal that epilepsy could be surgically treated. In 1886, Victor Horsley, a surgeon who worked closely with John Jackson, performed the first surgical operation to remove an epileptic focus. The patient was a 22-year-old man who had been experiencing epileptic motor seizures since the age of 7, following a head injury. The concept of motor homunculus had already been formulated at that time, and the post-traumatic scar was located in the same area as the focus of motor activity causing the seizures; thus, the corresponding area of the motor gyrus was removed. The epileptic seizures stopped following the surgery. Therefore, the feasibility of surgical treatment for epilepsy has been demonstrated [35]. Although brain interventions were associated with numerous complications, it was not always feasible to determine the focus localization, particularly in multifocal epilepsy, which resulted in the predominance of pharmacological treatment for epilepsy.

Several medications have been proposed and tested to suppress epileptoid activity. The first drug used in epilepsy therapy was potassium bromide. Its antiepileptic properties, which include reducing the frequency of seizures, were accidentally discovered by Wilks in 1857. Later, in 1888, Kovalevsky noted a positive effect of long-term use of lithium bromide [2].

The anticonvulsant effect of phenobarbital was discovered in 1912. It was widely used for treating epilepsy and was the drug of choice until 1960 [14]. In the 1940s, phenytoin, a barbiturate derivative whose efficacy had been demonstrated as early as 1938, began to be used. Unlike bromide compounds and phenobarbital, phenytoin did not have a pronounced sedative effect. Later, in addition to actively searching for pharmacologically related barbiturate compounds with anticonvulsant activity, studies were conducted on chemical compounds from other groups. These studies led to the development of three generations of anticonvulsant drugs [2].

The first generation of anticonvulsant drugs includes barbiturate derivatives. The second generation, which emerged between 1960 and 1975, includes carbamazepine, valproate, and benzodiazepines. These drugs are chemically unrelated to barbiturates. The third generation of anticonvulsant drugs, developed in the 1980s, are targeted agents that focus on critical mechanisms of epilepsy development [1]. Further development of pharmacotherapy requires an improved

understanding of the biochemical nature of changes in the epileptic focus. The development of physiology has made it possible to form an idea of action potentials and synaptic transmission, and the appearance of EEG has resulted in identifying differences in the electrical activity of the epileptic focus and intact cortical areas. This led to investigating the characteristics of the generation of action potentials in epileptic neurons and the function of their ion channels and neurotransmitter receptors [2].

Channelopathies has been found to cause epilepsy. Genetic abnormalities in ~1000 genes associated with the development of ion channels and neurotransmitter receptors may lead to the development of epilepsy. Metabolic abnormalities are often associated with these abnormalities, and epilepsy is one of the symptoms [13].

The symptomatic treatment of epilepsy with anticonvulsants typically involves one or more of the following mechanisms of action:

1) Modulation of potential-dependent channels, such as sodium channels (phenytoin, carbamazepine), calcium channels (ethosuximide), and potassium channels (retigabine)
2) Enhancement of GABA-mediated inhibitory transmission by activating GABA receptors (benzodiazepines)
3) Suppression of glutamate receptors (perampanel)
4) Modulation of neurotransmitter release via presynaptic action (levetiracetam) [36]

Epilepsy is treatable with medication; however, up to 70% of patients with focal epilepsy, particularly temporal localization, may be resistant to drug therapy [37, 38]. In these cases, non-drug therapies, such as a combination of a sodium channel modulator and a drug with GABAergic properties [39], ketogenic diet, brain electrical stimulation, gene therapy, or surgical methods [13, 40], may be considered.

## METHODS OF VISUALIZATION OF EPILEPTOGENIC FOCI

The EEG method was the first technique used to diagnose and locate epileptic foci. Its history dates back to 1875 when Carton recorded electrical potentials in the open cortex of rabbits and monkeys. In the 1920s, Berger published studies on the registration of electrical potentials from the human scalp and open cortex [41, 42]. In the 1930s, neurologists Lennox and Gibbs became interested in the method and described the patterns of different types of epileptic seizures [43, 44]. Since 1930, Penfield and Jasper began performing surgical removal of epileptic foci with preliminary determination of their localization using EEG. Percutaneous and cortical EEG and deep electrodes were used [45]. Surgical removal of the epileptogenic zone using EEG mapping remains one of the most effective methods for treating pharmacoresistant epilepsy [46-48].

In 1895, the discovery of X-rays by Roentgen led to the emergence of neuroimaging as the next stage in the study of epileptic foci [49]. One of the earliest neuroimaging techniques was pneumoencephalography, which was invented by Dandy in 1918. The method involves visualizing the brain ventricles and other liquor-containing spaces using X-rays after injecting air into the dural sac. This allows for outlining the boundaries of the brain's ventricular system on the X-ray image [50]. However, the technique was found to be painful in some cases and was associated with complications.

The development of X-ray contrast agents and the introduction of angiographic studies have enabled the visualization of cerebral vessels. Subsequently, angiographic techniques were used in conjunction with pneumoencephalography [49].

The invention of X-ray computed tomography (CT) by Hounsfield in 1968 revolutionized the understanding of central nervous system diseases. It made it possible to differentiate between various brain structures and the boundaries of gray and white matter. This included the ability to visualize epileptic foci. In 1976, the authors have identified foci of organic brain lesions causing epilepsy in 2/3 of the 1702 patients [49].

In 1973, Paul Lauterbur developed magnetic resonance imaging (MRI) [51]. However, despite its potential, MRI was not immediately appreciated in comparison with CT. It was not until 1980 that the first MRI study of a patient's brain was conducted. Difficulties in interpreting MRI images meant that it was not until 1992 that sufficient data had been accumulated to prove the advantages of MRI over CT in patients with epilepsy. The possibility of visualizing sclerotic changes in the hippocampus, associated with epileptic foci, played a significant role. Additionally, the ability to visualize small anomalies of cortical development was determined later [52].

According to the European Consensus Statement (2005/2021), diagnosing epilepsy requires clinical and EEG and MRI data [53, 54]. Meta-analyses indicate a high probability of seizure disappearance or reduction after surgery if MRI identifies the area of change [55–57]. However, surgical intervention may be less effective in cases where there are no organic changes


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on MRI or where EEG and MRI data are inconsistent. In such cases, surgical intervention is often delayed, which can lead to an increase in clinical symptoms, secondary foci formation, and complications in localizing epileptic foci and surgical treatment [55].

In atypical or clinically ambiguous cases, the gold standard for diagnosing epileptogenic foci is intracranial EEG. This method is highly invasive and associated with a risk of surgical complications. In some cases, it may not reliably identify epileptic foci because its sensitivity decreases in the presence of multiple sources of epilepsy. Thus, the search for noninvasive methods to determine the localization of epileptogenic activity foci or a combination of different studies within the framework of hybrid technologies or complex analysis remains an urgent issue.

Functional MRI, MR spectroscopy, and hybrid Subtraction Ictal SPECT Co-Registered to MRI (SISCOM) and PET/CT techniques to locate epileptoid foci have been investigated in the last decade. However, the PET/CT method has several disadvantages, including low anatomical detail of small brain structures and excessive radiation exposure from X-ray CT. The modern hybrid PET/MRI method eliminates these disadvantages by enabling the simultaneous study of both functional and anatomical features of the brain [61].

## SISCOM METHOD

During a seizure, blood flow increases in the epileptic focus. This allows for brain perfusion scintigraphy to be performed on a patient either during the seizure or immediately after. The onset of the seizure can be determined by clinical manifestations, such as a convulsive seizure, or by EEG data if the seizure is asymptomatic. MRI data obtained immediately after scintigraphy can be used as a structural and anatomical map in such cases.

The SISCOM method is a diagnostic technique that combines subtractive ictal single-photon emission computed tomography (SPECT) with MRI. It involves subtracting interictal SPECT perfusion data from ictal examination data and comparing the results with MRI data [37, 62]. SISCOM is not a standard method for the preoperative localization of the epileptic focus. However, it can provide additional information on the exact localization of the focus, which is crucial when MRI does not detect any pathological changes. In this case, radiopharmaceuticals based on $^{99m}$Tc-labeled hexamethylpropylene amine oxime (HMPAO) or ethyl cysteinate dimer are commonly used [59]. Currently, only radiopharmaceuticals based on $^{99m}$Tc-HMPAO are used in Russia.

During the interictal period, the epileptic focus exhibits either reduced or normal perfusion. However, during an attack, it is visualized as the focus of hyperperfusion. Localization of the focus in the presence of pathological changes significantly correlates with PET and MRI data [48, 59]. In some cases, perfusion changes can be visualized contralaterally to the actual primary focus. In 2002, So has reported a case in which focus resection detected by SPECT in a 14-year-old boy with convulsive seizures and loss of consciousness resulted in the improvement of clinical symptoms. After resection, epileptic seizures no longer caused fainting. These areas of hypoperfusion may correspond to secondary epileptic foci, which explains the partial improvement in the clinical picture after resection [63].

Figure 3 shows SISCOM images of a patient's brain with complex partial seizures, indicating increased perfusion in the anterior pole of the right temporal lobe, primarily in the medial region [64].

## MAGNETIC RESONANCE IMAGING, FUNCTIONAL MAGNETIC RESONANCE IMAGING

The International League Against Epilepsy Commission on Diagnostic Techniques indicates that brain MRI in epilepsy should include T1-weighted images in three projections, T2-weighted fluid-attenuated inversion recovery, and a spin echo

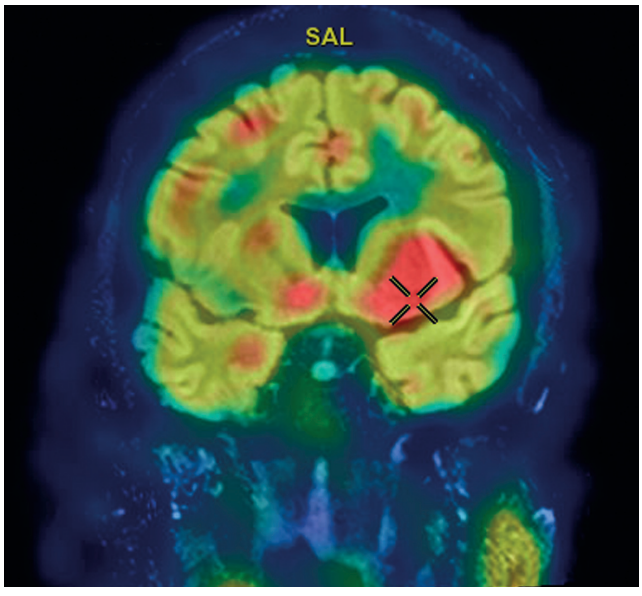


**Fig. 3.** A fused SISCOM image (SPECT of the brain performed during a complex partial seizure combined with MRI of the brain) demonstrating hyperperfusion in the basal ganglia and insula of the left hemisphere (courtesy of FSBI «FCMN» FMBA of Russia).

sequence in the oblique projection perpendicular to the long axis of the hippocampus. Further, T1-mode studies should be performed after the administration of gadolinium-containing contrast agents [65].

The recommended magnetic field strength for an MRI scanner is 3.0 Tesla. However, studies can also be performed on a scanner with a magnetic field strength of 1.5 Tesla. Notably, spatial resolution may be insufficient to detect some clinically significant structural changes, such as small areas of focal cortical dysplasia [66].

Functional MRI can increase the informativeness of a study. This technique is based on the Blood Oxygen Level Dependent (BOLD) imaging effect, which relies on the difference in hemoglobin properties between its oxygenated and deoxygenated states. Oxygenated and deoxygenated hemoglobin concentrations in the blood affect MRI signal intensity.

Activation of nerve centers during a test task results in a local increase in blood flow in the corresponding area of the brain, leading to a slight increase in the BOLD signal due to an increase in hemoglobin oxygen saturation. Functional MRI is used for preoperative mapping of various functional centers in the brain and for planning surgical treatment. This type of study requires specialized equipment [67].

The most frequent changes detected on MRI in patients with epilepsy in the epileptic focus area are hippocampal sclerosis (44.5% in adults, 15.0% in children), brain tumors (23.6%), and cortical malformations (20.0% in adults, 39.3% in children). Focal cortical dysplasia, the most common congenital malformation, accounts for up to 70.6% of all cortical developmental anomalies. Moreover, MRI can detect other cortical abnormalities, such as polymicrogyria and gray matter heterotopia, vascular malformations, glial scarring, infectious changes, and other alterations [67, 68]. In 30%–50% of patients with epilepsy, structural changes cannot be identified on MRI or there is a mismatch between MRI findings, EEG data, and clinical presentation [69, 70]. Radiological methods can be used to localize the epileptic focus and assess its resectability. These methods include PET and the new hybrid PET/MRI method. The hybrid method allows for a more detailed MRI study of the brain structure in the hypometabolic areas detected by PET and the detection of subtle changes [71].

## POSITRON EMISSION TOMOGRAPHY OF THE BRAIN

PET with $^{18}$F-FDG is commonly used for diagnosing epileptic foci owing to its effectiveness and availability. PET has been used to study abnormalities in $^{18}$F-FDG metabolism in epileptic foci for over three decades [72]. The drug is administered intravenously and can easily penetrate the blood–brain barrier. Once in the brain, it enters neurons and is phosphorylated by hexokinase, which turns into 18F-deoxyglucose-6-phosphate. Unlike the glucose metabolite glucose-6-phosphate, this compound does not participate in further reactions of ATP synthesis and accumulates in cells [73].

During the interictal period, the epileptic focus is identified on PET images as a hypometabolic zone. Epileptic foci lack areas of hypermetabolism during this period, and decreased $^{18}$F-FDG accumulation in potential foci are sensitive but nonspecific to epilepsy. Therefore, PET data should be interpreted with CT or MRI data to visualize structural changes in areas of hypometabolism [72, 74].

PET imaging during an epileptic seizure has several limitations, including uncontrolled patient movement. However, few studies have been published on this topic. Additionally, the radiopharmaceutical $^{18}$F-FDG has a half-life of 110 min and requires at least 30 min for distribution and accumulation in cells. In most protocols, the period between the administration of radiopharmaceuticals and the start of the examination is 60 min [29]. The main challenge in recording an ictal PET examination is the practical impossibility of predicting the onset of an epileptic seizure an hour before it occurs. Studies have reported instances of unintentional registration of ictal PET, where the onset of a seizure is typically determined by EEG recorded simultaneously with PET. During the ictal period and for a period thereafter, there is a significant increase in FDG metabolism in the epileptic focus compared with that in the unchanged brain parenchyma [63].

In 1994, Chugani and Conti [29] have classified hypermetabolic changes detected by PET during epileptic seizures. Of the 139 children examined, 18 showed signs of unanticipated epileptic seizures, and hypermetabolism foci were recorded on PET. The authors identified three primary groups of foci: those with asymmetric areas of increased $^{18}$F-FDG accumulation, those with symmetric hypermetabolism, and those with unchanged $^{18}$F-FDG metabolism in the striatum and thalamus but changes in other areas. Some patients exhibited signs of epileptic seizure on EEG but no $^{18}$F-FDG hypermetabolism. In these cases, the seizure began at least 20 min after $^{18}$F-FDG administration, was brief, and was not accompanied by convulsions [29].


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The decrease in $^{18}$F-FDG metabolism in the epileptic focus during the interictal period and the increase during the ictal period correlate with the SISCOM data. Hypoperfusion was observed in the focus during the interictal period and hyperperfusion during the seizure. PET detects a larger focus size than MRI, EEG, and SISCOM in most comparative analyses [48, 59].

A study of $^{18}$F-FDG metabolism within 48 h after a seizure in patients with prolonged interictal period showed an increase in metabolism during the first 24 hours, peak accumulation on the second day, and a return of metabolism to baseline values after 48 hours [30]. Glucose hypometabolism is often detected on PET in the presumed epileptic focus during the interictal period, with localization of the metabolic zones corresponding to structural changes on MRI in 75% of cases. Surgical intervention can achieve remission in several patients with pharmacoresistant epilepsy (up to 90% in the absence of additional foci of hypometabolism located outside the resection area) if the localization of the epileptic focus coincides with the EEG and PET data [59, 73, 75, 76].

In cases of MR-negative epilepsy, PET can be used to identify hypometabolic areas and revise MRI data in corresponding brain regions, thereby detecting subtle structural changes. This is particularly critical for small focal cortical dysplasias. Although some of the hypometabolism foci detected are not confirmed by MRI data, surgical resection of this area using intracranial EEG in most cases leads to an improvement in clinical symptoms, up to the complete disappearance of seizures. Additionally, in some patients (up to 30%), an MR-negative epileptic focus is visualized contralaterally to EEG data. In such cases, EEG data (intracranial EEG) is crucial [37, 59] (Fig. 4).

The visualized area of $^{18}$F-FDG hypometabolism is distinct as it often extends to the ipsilateral frontal and parietal lobes, significantly exceeding the actual size of the epileptogenic focus. Therefore, PET results should be compared with anatomical data, especially in the preoperative planning of patients with pharmacoresistant epilepsy. In a hybrid PET/CT study, CT data can be used to locate the hypometabolic focus anatomically. However, because of insufficient tissue contrast, it is difficult to visualize the zone of structural changes that correspond to the epileptic focus on CT scans. Moreover, CT studies are associated with additional radiation exposure.

The hybrid PET/MRI method can improve the diagnostic accuracy of epileptic foci. Currently, it is of scientific interest [32, 33]. Although hybrid PET/MRI scanners are being actively improved [77, 78], they have

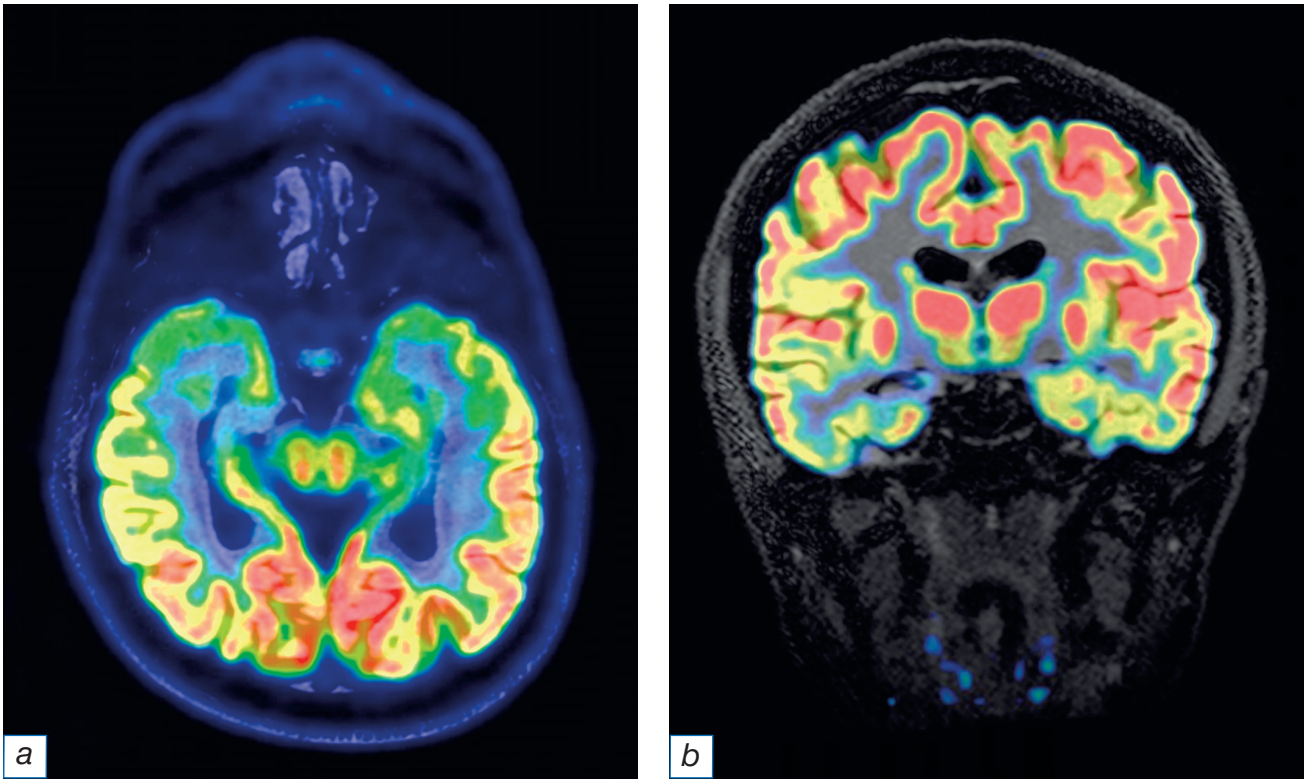


**Fig. 4.** Combined positron emission tomography combined and fLAIR images obtained in the axial (*a*) and coronal (*b*) planes. Significant reduction of the $^{18}$F-FDG uptake is noted in the right hippocampus head and corpus (courtesy of FSBI «FCMN» FMBA of Russia).

not been widely used to date, and their role in epilepsy diagnosis remains to be established. Importantly, a scanner can often obtain data from both PET and MRI studies simultaneously. This is unlike PET/CT scanners, in which PET and CT data are recorded sequentially. This feature of data acquisition ensures that all data are recorded at each moment of the study, allowing for the simultaneous recording of structural, anatomical, and functional parameters [79].

The first hybrid PET/MRI scanners were installed in clinical centers in 2009–2010 [80]. One of the main challenges of combining PET and MRI scanners was the interference created by scintillator radiation in positron emission sensors [81]. The technical difficulties faced by creators of scanners have been overcome in two ways: by removing the gentries for PET and MRI examinations to a sufficient distance and by changing the properties of PET detectors. The Philips Ingenuity TF PET/MR system used the first method, which involved separate PET and MRI tomographs positioned 2.5 m apart. The patient was moved sequentially on a mobile table from examination to examination; however, this approach resulted in the loss of the advantages of a one-stage examination [82]. The second technical method was first implemented in the Biograph mMR Siemens tomograph. Avalanche photodiodes were used as PET detectors in this case, which significantly reduced the interference between the two types of detection. Several separate PET gentri rings were installed between the MRI sensors, enabling the simultaneous performance of two examinations [77]. Currently, this system is the most widely used.

Hybrid PET/MRI has higher sensitivity and specificity in detecting epileptogenic foci compared with analyzing MRI and PET diagnostic data separately [32, 79]. Specifically, $^{18}$F-FDG-PET is more effective than MRI in detecting small malformations, such as focal cortical dysplasia, which are identified by PET in 60%–80% of cases and by MRI in only 33%. Joint registration of PET and MRI enabled the localization of hypometabolic zones in 46% of MRI-negative patients and confirmed 12% of doubtful MRI results. This increases the detection rate of focal cortical abnormalities by up to 94% [83]. The possibility of revising MRI data when metabolic abnormalities are detected allows for the detection of small structural changes that were previously undetected or underestimated.

Importantly, $^{18}$F-FDG is phosphorylated by hexokinase once it enters the neuron and does not undergo further glucose metabolism. This may be significant for patients sensitive to a ketogenic diet because an increase in glucose levels is associated with a higher likelihood of developing epileptic seizures. Therefore, $^{18}$F-FDG has been identified as a glycolysis inhibitor during the ketogenic diet [84].

Compared with the selective analysis of PET and MRI, the use of hybrid PET/MRI increases the detection rate of focal cortical dysplasia, provides additional prognostic information, and allows the detection of changes not determined by each method separately [85]. Further, a unilateral decrease in $^{18}$F-FDG uptake in temporal lobe epilepsy is characterized by a more favorable prognosis of surgical treatment.

Several studies have suggested the use of radiopharmaceuticals other than $^{18}$F-FDG in PET/MRI. For instance, $^{11}$C-flumazenil reduces $^{11}$C-flumazenil accumulation in the epileptic focus. However, meta-analysis data indicate that PET examination with $^{11}$C-flumazenil is not more accurate than that with $^{18}$F-FDG and only reflects the loss of neurons expressing benzodiazepine receptors [86]. Kaqawa et al. [87] have demonstrated an increased uptake of $^{11}$C-alpha-methyl-tryptophan by tuberculomas in children with tuberous sclerosis. The use of $^{11}$C-PK11195 radiopharmaceutical has been demonstrated to enhance the precision of epileptic focus localization in tuberous sclerosis, thereby increasing the possibility of a positive outcome of surgical treatment. Additionally, $^{11}$C-PK11195 can be used to locate foci in Rasmussen's encephalitis, which is characterized by neuroinflammation and activation of microglia that synthesize a specific translocator protein that binds to $^{11}$C-PK11195. Consequently, this radiopharmaceutical can be used to detect epileptic foci in Rasmussen's encephalitis and other epileptiform conditions [88]. Moreover, $^{18}$F-FCWAY, which is a 5-HT1A receptor antagonist, has been indicated as a potential solution. Serotonin mediates anticonvulsant effects via 5-HT1A receptors. Therefore, areas with decreased $^{18}$F-FCWAY accumulation indicate a reduction in the number of these receptors, making it possible to identify regions with an increased likelihood of epileptic seizure development [89].

Additionally, some studies have shown the feasibility of perfusion PET using $^{15}$O [29]. However, this method has not gained widespread use because of the short half-life of the radionuclide and need for an in-house cyclotron.

A novel technique called dynamic PET with $^{18}$F-FDG has been presented. Unlike static PET, which only reflects the total glucose uptake over a certain time interval (5–20 minutes), dynamic PET reflects a continuous change in volumetric radioactivity. Scanning begins


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before the administration of radiopharmaceuticals, and the indicator is administered during the scan. Data collection proceeds as a series of scans, recording changes in $^{18}$F-FDG concentration throughout the scanning interval. In studies using $^{18}$F-FDG PET to examine patients with epilepsy, kinetic processes may be a differentiating factor. Abnormal tissues may have higher or lower hexokinase concentrations or differences in enzyme function, which can result in higher or lower $^{18}$F-FDG accumulation rates and changes in the glycolysis rate profile compared with normal tissues [72]. Dynamic PET is scientifically and practically interesting and appears promising because of the developing technologies, fast data acquisition, and high-quality processing of hybrid examinations.

## CONCLUSIONS

The understanding of the origin, diagnosis, and treatment of epilepsy has undergone significant changes. Currently, the precise localization of the epileptic focus and evaluation of its resectability remain relevant issues. The accuracy of diagnosis is crucial for the surgical treatment of patients with pharmacoresistant epilepsy.

Although there are several diagnostic techniques available, the best algorithm for the preoperative examination of epilepsy patients remains debatable. The hybrid PET/MRI method provides additional information on the localization of epileptic foci, is more sensitive and specific in detecting small anomalies of cortical development compared with selective PET or MRI, and allows for a shorter examination time compared with performing PET and MRI separately. This is more comfortable for patients and allows researchers to study rapid processes simultaneously. When conducting a study using modern PET/MRI devices, anatomo-morphological data and functional brain activity are analyzed simultaneously. This guarantees full correspondence of the obtained images and excludes changes in structural abnormalities over time.

Further study of the possibilities of the hybrid PET/MRI method is of scientific interest because it can improve the surgical treatment results of patients with pharmacoresistant epilepsy.

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