Clinical Value of Functional MRI in the Diagnosis of Cognitive Disorders in Patients with Arteriovenous Malformations

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Abstract: Cognitive impairment that develops in acute and chronic cerebral pathology, including arteriovenous malformations, is one of the most frequent and prognostically unfavorable complications. Late detection of severe forms of cognitive impairment, including dementia, leads to a lack of early preventive and therapeutic correction, a decrease in the effectiveness of rehabilitation and the quality of life of patients with AVM. A comprehensive assessment of cognitive impairment may be a diagnostic criterion for assessing the severity of neurological symptoms at the endovascular treatment stages. A significant contribution to the study of the pathophysiology of CN formation in patients with AVM is made by fMRI, providing knowledge about the functional organization of the brain. The results of functional mapping of the brain in 11 patients with arteriovenous malformations are presented. The structure of cognitive impairment was evaluated using advanced neuropsychological testing and structural-functional restructuring in the cerebral cortex using fMRI. To obtain images, an echoplanar tomography technique using BOLD contrast was used. The data obtained indicate complex neurodynamic disorders of the cognitive sphere in patients with AVM in several areas of both the right and left hemisphere: dorsal, ventral and medial front-striatal thalamic and fronto-parietal cerebellar networks.

1 INTRODUCTION

Cerebral arteriovenous malformations (AVM) are a malformation of cerebral vessels belonging to the group of congenital and progressive vascular diseases of the central nervous system (Robert,2007; Berman, 2007; Lin et al, 2012).

AVMs are a significant source of disability and mortality in the working age population among various forms of cerebrovascular abnormalities. Up to 4% of all intracranial volume formations, 9% are causes of non-traumatic subarachnoid hemorrhages, 1% are ischemic strokes (Robert, 2017).

Information on the frequency of occurrence of cerebral AVM in the population is contradictory and depends on the sources of information. Some studies indicate that the prevalence of the disease in the adult population is 19 per 100,000 people, and the frequency of surgical interventions for AVM of the cerebral vessels is 0.9 per 100 thousand of the population per year (Laakso et al., 2010; Lunsford, 2009; Laakso et al. A2012).

The clinical manifestation of AVM most often occurs in people 20-50 years old, and the long-term prognosis without surgical treatment is unfavorable: 23% of patients die, in 48% the disease leads to disability, which indicates the social significance of this problem (Robert, 2017).

One of the most frequent and maladaptive manifestations of AVM is cognitive impairment (CI) (Marshall et al., 2003; Steinvorth et al., 2002, Lazar et al. 1996; Steinvorth, 2002; Andrea et al.,2014; Buklina, 2001).

Considering that AVM is a congenital pathology, CI at the stage of mild disorders often remain underestimated, thereby transforming into more severe forms, leading to significant limitations in work, the social sphere, and patient self-care (Ernst et al.,2017; Charidimou et al., 2017)

The cerebral cortex is a complex integrated system that combines a large number of different parts of the nervous system, each of which performs

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a specific function. At the same time, these departments interact with each other, participating in the implementation of one or another program, in the framework of which the information entering the brain is constantly processed by centers structurally and functionally interconnected (Yakhno et al., 2014; Luria, 2000, Mendoza et al., 2014)

The quantitative and qualitative characteristics of cognitive impairment are extremely important in the diagnostic work of neurologists, neurosurgeons, therapists and doctors of other specialties. The identification and clinical analysis of the cognitive impairment features in patients with AVM is necessary for the correct syndromal and topical diagnosis, for assessing the severity of neurological symptoms at the stages of endovascular treatment of AVM. Extensive neuropsychological testing and conventional neuroimaging are not enough to describe the general picture of AVM, because even if it can provide accurate anatomical localization, it does not provide any information about the functional organization of the brain.

A significant contribution to the study of the pathophysiology of cognitive impairment formation in patients with AVM is made by modern methods of neuroimaging, one of which is fMRI, because it allows you to simultaneously obtain data on metabolism, blood flow and structural and functional characteristics of the brain (Ellis, 2016).

The first work on the use of fMRI in brain research appeared in 1992 (Bandettini, 1992). FMRI has become the standard for determining the activity of brain neurons in humans, since it is a non-invasive method, has reliable localization of responses, and high spatial resolution, compared to the earlier developed technologies, such as positron emission tomography (PET) (Odinak, 2006; Lazar et al., 2010).

Considering that the hemodynamic characteristics of AVM is a decrease in pressure in the arteries involved in the blood supply to AVM, a unified system of blood circulation equilibrium is being displaced, and as a result — arteriovenous bypass surgery has a damaging effect on the cerebral cortex. According to the mechanism of intensive venous discharge, areas of reduced microcirculation are formed, both in the affected vascular pool and in the opposite hemisphere. Due to the structural and functional reorganization of the cerebral cortex, that occurs against the background of insufficient blood circulation, cortical functions from certain parts of the brain are rearranged to adjacent parts of the brain, which leads to their later manifestation in patients with AVM (Ishikawa et al., 2017; Moretti et. Al., 2017).

Functional magnetic resonance imaging is considered as a way of studying the "functional architecture" of the brain. The most widely used fMRI technique is based on the sensitivity of the pulse sequence of the gradient echo to changes in the oxygenation of brain tissue - the BOLD effect (Barbay et. al., 2017, Keefe et. al., 2017).

With this sequence, changes in the magnetic resonance signal in the same part of the brain under conditions of rest and activation occur due to differences in the paramagnetic properties of deoxyhemoglobin and oxyhemoglobin. It is believed that when exposed to an irritant, the degree of increase in regional blood flow exceeds the tissue's oxygen demand, which leads to local hyperoxemia and, consequently, to a decrease in the concentration of deoxyhemoglobin. Due to a decrease in the degree of local inhomogeneity of the magnetic field, an increase in the magnetic resonance signal occurs. Areas that change the signal intensity in accordance with the shape and duration of the stimulus are detected using special statistical processing, are selected in the form of activation maps and combined with anatomical images of the brain.

Regarding the study of the cognitive status of patients with AVM, there are only a few studies. In 2013, a team of researchers led by R.L. Piana showed how the combined use of different imaging techniques can be useful in understanding neuroplasticity and hemodynamics in patients with AVM at the endovascular treatment stages. Valuable information in this case is that the structural and functional organization of the brain in patients with complex AVMs has a number of features, and it can be obtained using a more systematic and extensive imaging protocol that combines perfusion with complex analyzes of functional MRI (fMRI) and anatomical MRI for the purpose of mapping brain activations at the stages of endovascular treatment of vascular abnormalities (Roberta La Piana, 2013).

In the works of J.C. Lin, T.H.Le described cases of regression of neurological deficit after microsurgical removal of malformation due to compensatory rearrangement of cortical functions.

A study conducted in Japan between 1977 and 1994 described dynamic changes in activation zones for stimulus tasks. This pattern was presumably associated with either hemorrhage or ischemic disorders that correlated with changes in MRI (hemosiderin deposition, hypoperfusion zones associated with the “robbery phenomenon”) (Kida, 1994).

A number of foreign fMRI studies have shown that the functional activity of the cerebral cortex is specifically impaired in patients with depressive and anxiety disorders (Bremner et al., 2002; Cotter et al., 2001).

Using fMRI methods, Russian researchers have demonstrated the effects of activation of neuroplasticity under the influence of neuroelectrostimulation in patients with depressive disorder. The use of modern methods of data analysis of fMRI revealed a significant improvement in the functioning of the basic working network and brain connectivity in the studied patients (Kublanov, 2018; Kublanov, 2019).

To assess cognitive impairment in patients with AVM, a comprehensive examination is necessary, including not only the identification of structural changes using modern neuroimaging methods, but also a qualitative analysis of integrative changes using neuropsychological examination. In routine practice, CI in patients with AVM often remains unrecognized due to the lack of a standard examination protocol and the possibility of long-term monitoring of this category of patients (Skrobot et al., 2018; Behrman, 2017).

2 PURPOSE

The aim of our study was to assess the clinical significance of modern functional neuroimaging in the diagnosis of cognitive impairment in patients with arteriovenous malformations of the brain, who underwent embolization of the AVM with the non-adhesive ONYX composition.

3 MATERIALS AND METHODS

3.1 Study Population

The main criterion for inclusion in the study was the presence of AVM of supratentorial localization, confirmed by the history, neurological examination, and the results of a routine neuroimaging examination. The study included 11 patients with arteriovenous malformations of the brain who have been treated at the Russian National Pedagogical Institute. prof. A.L. Polenova from January 2014 to December 2017, who performed embolization of the AVM with the non-adhesive ONYX composition, and 18 healthy right-handed volunteers (healthy controls), who were stratified by gender and age. The average age of patients with AVM was 36.6 years. Analysis of the results was made with a maximum follow-up of 12 months. The structure of cognitive impairment was evaluated using advanced neuropsychological testing and structural and functional restructuring in the cerebral cortex using fMRI. To activate various areas of the cerebral cortex during fMRI, patients were asked to perform special tasks-paradigms. The following were used: the standard speech block paradigm (speech test), the generation of counting operations according to the indifferent counting series presented with the help of headphones (counting test), the activation of optical-spatial functions and visual memory using simple (non-plot) pictures presented on the screen (visual stimuli).

3.2 MR Imaging Protocol

To obtain images, we used the echoplanar tomography technique using BOLD contrast. Postprocessing included the elimination of artifacts, statistical analysis of BOLD signals, the construction and combination of t-maps of activation zones with T1 of the brain and their transformation into the MNI coordinate space (Montreal Neurological Institute - Montreal Neurological Institute). The study was performed using 1.5 Tesla MR scanner. The observations were dominated by the epileptic type of course - 8 (41.1%), hemorrhagic type was found in 3 patients (33.56%).

The majority of patients with AVM in the amount of 6 (54.5%) cases were assigned to Spetzler-Martin Grade III and V, with the exception of 1 (9.1%) patient of Grade IV. In the studied group of patients, AVM localization in the left hemisphere prevailed - 6 (54.5%) patients. Of these, in an amount of 4 (36.4%) in the left parietal lobe, temporal lobe -1 (9.1%), in the left occipital lobe -1 (9.1%). In the right hemisphere, the main localization of the AVM is in the parietal lobe and occipital lobe 2 (18.2%), in one case (9.1%) in the frontal lobe.

The principle of multi-stage, complex treatment was used in all patients - the maximum possible AVM fragments were embolized during one surgical intervention (60% approx. of the whole volume of AVM).

3.3 Results

When performing intragroup analysis (healthy volunteers) at the stages of interaction of neuronal structures for recognizing the presented images, a decrease in activation was detected in the prefrontal cortex, the Broadman area (BA) 10, as well as in the projection of BA17 and BA18 (MNI coordinates: -36 -

90 14). At the same time, an increase in activation was observed in the isthmus of the cingulate gyrus - BA31 (MNI coordinates: 6 -62 32), in the insula (MNI coordinates: 4 40 38) and the parahippocampal gyrus (MNI coordinates: 32 -36 -12). Local patterns of processing visual information, recognizing visual images and transmitting information to other departments of the visual analyzer that are involved in providing emotional-volitional decisions, the formation of motivation, cognitive flexibility, short-

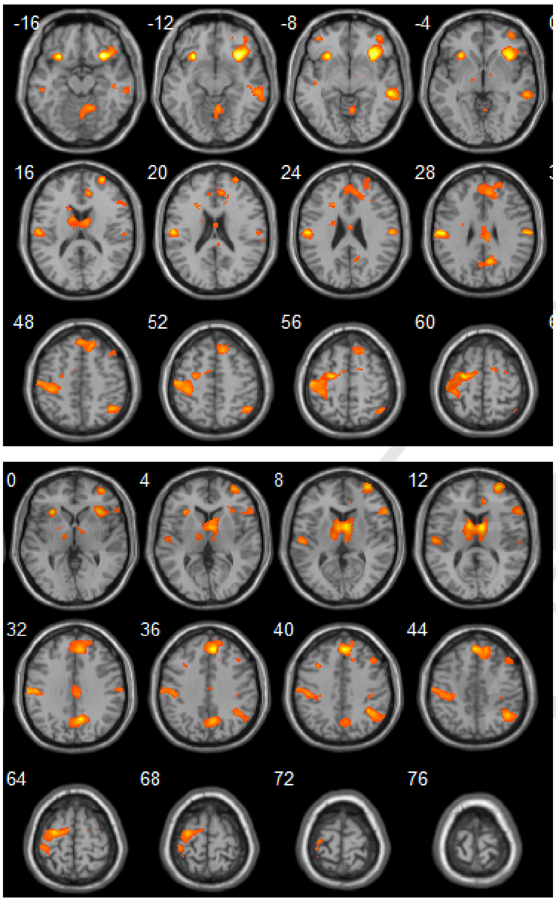

Figure 1: The control group. Activation sites (response to a visual stimulus) in the projection of brain structures: the isthmus of the cingulate gyrus, insular cortex, parahippocampal gyrus, Broca and Wernicke areas — bilaterally.

term memory and neurodynamics, which is the main function of the thalamo lenticular complex (Figure 1), were found. The topical importance of the parahippocapal complex is to create complex cognitive patterns, form short-term memory, while being the basis of neurodynamic thinking, forming connections with cortical, subcortical, stem formations of the brain.

As it can be seen in Figure 2, when performing a speech test, there were activations in the region of the parahippocampal complex in the projection of the fusiform gyrus (MNI coordinates: 30 -34 20), upper and lower temporal gyri on the right (MNI coordinates: 52 64 22; 54 -18 -22), upper frontal gyrus on the right, caudate nuclei (MNI coordinates: 6 8 -6), insular lobes (MNI coordinates: 34 -22 10).

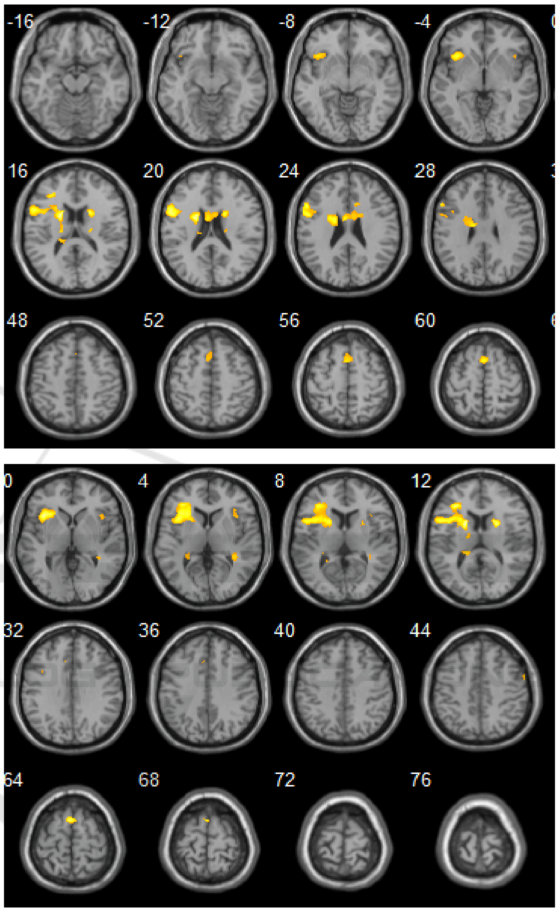

Figure 2: The control group. Activation sites (response to a speech test) in the projection of brain structures: the isthmus of the cingulate gyrus, insular lobes and parahippocampal gyri.

Presenting a "count" stimuli resulted in activation areas in the projection of the middle frontal gyri bilaterally, insular cortex on the right (MNI coordinates: 40 - 14 8), the upper frontal gyrus on the left (MNI coordinates: -14 48 48), precentral gyrus bilaterally (MNI coordinates: 38 -14 50; -24 -24 62). All these zones are parts of the working network of the brain at rest and carry out complex, including logical, processing of information of various nature, are responsible for short-term and long-term memory, fluency of speech, neurodynamics, and error control

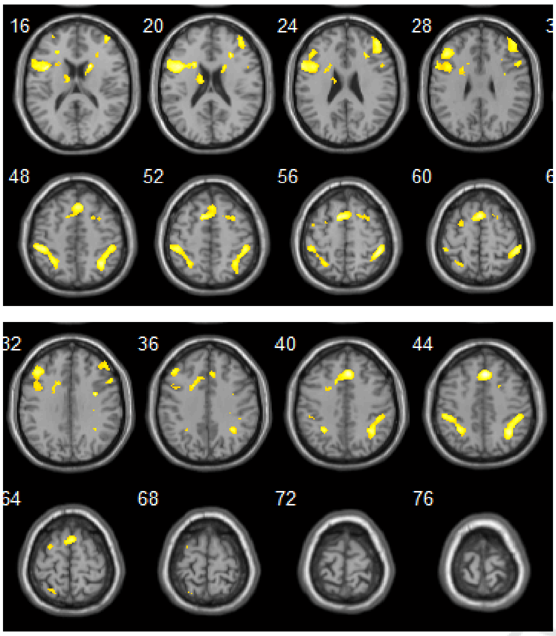

Figure 3: The control group. Activation sites (response to a count test): in the projection of brain structures: medial prefrontal cortex, BA9, BA46, BA31, BA32.

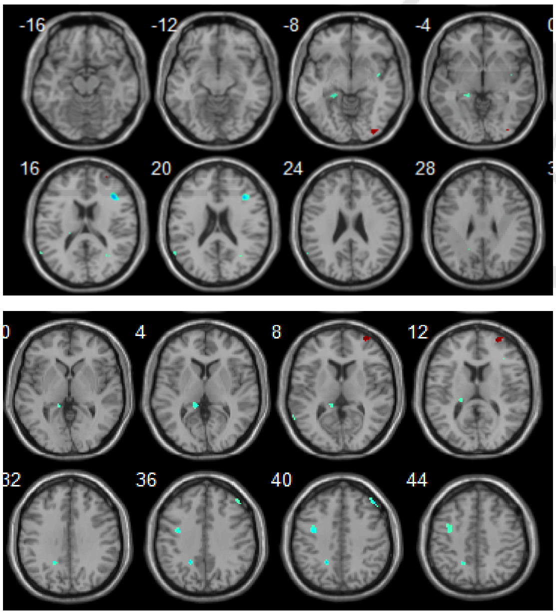

Figure 4: Results of intergroup analysis. Activation sites (response to the visual stimuli) presented in the patient group compared to the control group. Increased severity (blue): in the projection of PB 6, PB 10, parietal cortex, prefrontal and cingulate cortex, (p <0.001).

(Figure 3).

The dynamical intergroup analysis was aimed to establishing statistically significant differences between the volume of activations to compare functional changes in the cerebral cortex in patients with AVM and healthy volunteers. In patients with AVM, fewer activation sites were detected in response to certain cognitive tasks. Recognition of the presented images, storing and fixing of repeated images on the images presented on the screen revealed an increase in the activation of the following areas of the brain in patients with AVM: on the left is the region of the central gyrus, subcortical structures BA6 (MNI coordinates: -2 8 -25), BA10 (MNI coordinates: 23 55 7); parietal cortex (MNI coordinates: 23 -38 52), on the right - the lower parietal cortex (MNI coordinates: -24 -50 -40), the prefrontal cortex (MNI coordinates: 17 44 2) and the cingulate cortex (MNI coordinates: 4 23 22), p <0.001, (Figure 4).

When performing a speech test, in patients, comparing to the control group, a decrease in activation was found in the following areas: lower parietal lobe bilaterally, insular lobules on the left (BA13, MNI coordinates: -42 4 -1), lower frontal gyrus on the left (MNI coordinates: -32 47 -1), caudate nucleus (MNI coordinates: 14 10 11) on the left, parahippocampal gyrus on the left (MNI coordinates: 24 -9 -4). There was also a statistically significant increase in activation in the projection of the superior frontal gyrus on the left (BA 10, MNI coordinates: 12 49 4), the medial prefrontal cortex and the anterior cingulate gyrus, p <0.001, (Figure 5). The main functions of these zones are organization of complex cognitive circuits, the substrate of short-term memory, the basis of neurodynamic thinking. They form connections with cortical, subcortical, stem structures in the brain.

When performing count test (repeated count operations), in patients, comparing to the control group, a statistically significant increase in activations was established in the following areas: inferior parietal lobe, BA32 bilaterally (MNI coordinates: -10 46 11; 14 40 11) , BA7 (MNI coordinates: 23-60 60), BA9 on the right (MNI coordinates: 35 39 31), insula (MNI coordinates: 44 4 10), middle frontal gyrus (MNI coordinates: 30 47 11), waist gyrus on the left (MNI coordinates: -3 36 11), p <0.001, (Figure 6).

In the structure of cognitive impairment within the group of patients with AVM at the stages of endovascular treatment (ONYX embolization), cognitive impairments of a mixed structure (dysfunction of the fronto-subcortical formations of the brain; structures of the hippocampal circle; temporal-parietal-occipital region) were revealed - 90%; dysfunction of the structures of the hippocampi - 10%. In 70%, cognitive impairment was noted at the

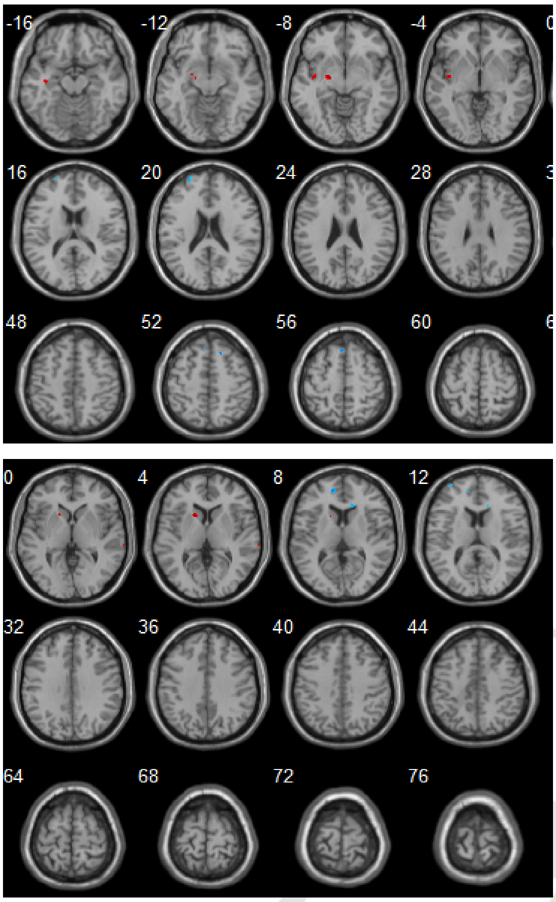

Figure 5: Intergroup analysis results. Activation sites (response to the presented speech test) in the patient group compared to the control group. Increased (blue): in the projection BA10 on the left. Decrease (red): in the projection of the lower frontal gyrus on the left, the insula on the left, the caudate nucleus, the parahippocampal gyrus on the left (p <0.001).

level of the first functional block (block of regulation of brain activity) - nonspecific structures of the brain (thalamo-reticular complex) and the third functional block (level of regulation, control of activities). In all patients in the group with AVM, a defeat of the second functional block (block of reception, processing and storage of ectoceptive information (modally specific processes) was noted. Focal neurological symptoms in the form of oculomotor disorders, homonymous hemianopsia and coordinating disorders were revealed in 60% of cases. About 30% of patients showed mild hemiparesis and pyramidal symptoms, and 20% had Vincent's symptom (BA4, BA6) and mild sensitive disorders.

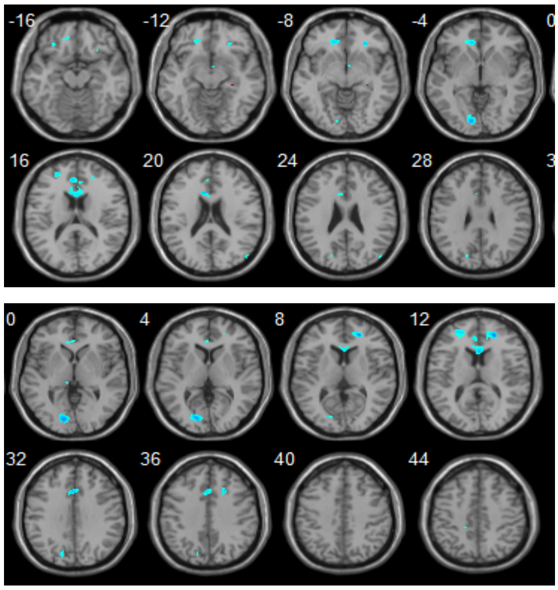

Figure 6: Intergroup analysis results. Activation sites (response to the presented sample test) in the patient group compared to the control group: Increased (blue): in the projection, left inferior parietal lobe BA9, left middle frontal gyrus (p <0.001).

4 CONCLUSIONS

The clinical significance of modern functional neuroimaging plays an important role in the diagnosis of cognitive impairment. The results of our fMRI study in patients with AVM using the diagnostic algorithms indicate complex neurodynamic disorders of the cognitive sphere in several areas, such as the right and left hemispheres of the dorsal, ventral and medial fronto-striato-thalamic and fronto-parieto-cerebellar networks, responsible for control, attention, reaction speed of choice. In addition, there is growing evidence of a decrease in activation in patients with AVM at the endovascular treatment stages in the prefrontal and limbic regions, which provide motivation and control of emotions. Pathogenetic features of cognitive impairment, assessment of modern methods of neuroimaging and diagnosis using advanced neuropsychological testing are currently a promising area. However, features in the field of correlation between functional research methods and early identification of cognitive impairment using advanced neuropsychological testing have not been investigated. The study of the structure of cognitive impairment using fMRI in combination with neuropsychological testing can help take a fresh look at the vast neuronal relationships in the central nervous system. The inconsistency of numerous literature data confirms the relevance of this technique to improve the diagnosis of cognitive impairment in patients with AVM in order to optimize the therapeutic effect.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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