

## STUDY OF FUNCTIONAL CEREBRAL CONNECTIVITY FOR THE DEVELOPMENT OF TREATMENT AND PREVENTION STRATEGIES IN PATIENTS WITH ASYMPTOMATIC CAROTID ATHEROSCLEROTIC STENOSIS

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**Abstract.** The aim of the study was to investigate the condition of the connectome in patients with asymptomatic carotid atherosclerotic stenosis of more than 60% when using hirudotherapy.

**Materials and research methods.** The examination results of 15 patients aged 60 to 82 years with asymptomatic carotid atherosclerotic stenosis in the range of 60-75% were analyzed. The patients underwent a course of hirudotherapy of 10 sessions. All patients underwent structural and functional magnetic resonance imaging with statistical data analysis at rest, complaints and neurological status were evaluated before and after hirudotherapy course.

**Results of the study and their analysis.** Within the course of hirudotherapy in patients with asymptomatic carotid atherosclerotic stenosis when analyzing the neurological status and complaints, a significant improvement of well-being was noted. Functional magnetic resonance imaging identified differences in functional connectivity between medial prefrontal cortex and other brain regions. There was activation in the main structures of the network of controlling and revealing significance. The connectivity between the leading areas of the brain increased, which is a sign of the improvement of the brain activity.

**Conclusion.** The study of connectivity can serve for exploring the work of brain networks and for determining the effectiveness of therapy. A course of hirudotherapy significantly changed the functional connectivity of brain areas, the changes correlated with a decrease in the number of complaints. Such work is a pilot and will be continued in order to further develop treatment and prevention strategies with the inclusion of hirudotherapy in patients with high risk of vascular accidents in sanatorium-resort treatment.

**Key words:** atherosclerotic stenosis, asymptomatic carotid hirudotherapy, brain, connectome, functional connectivity, magnetic resonance imaging, patients, therapeutic and preventive strategies

**Conflict of interest.** The authors declare no conflict of interest

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## ИЗУЧЕНИЕ ФУНКЦИОНАЛЬНОЙ КОННЕКТИВНОСТИ ГОЛОВНОГО МОЗГА ДЛЯ РАЗРАБОТКИ ЛЕЧЕБНО-ПРОФИЛАКТИЧЕСКИХ СТРАТЕГИЙ У ПАЦИЕНТОВ С АСИМПТОМНЫМ КАРОТИДНЫМ АТЕРОСКЛЕРОТИЧЕСКИМ СТЕНОЗОМ

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**Резюме.** Цель исследования – изучить состояние коннектома у пациентов с асимптомным каротидным атеросклеротическим стенозом (АКАС) более 60% при применении гирудотерапии.

**Материалы и методы исследования.** Проанализированы результаты обследования 15 пациентов в возрасте от 60 до 82 лет с АКАС в пределах 60-75%. Пациентам проводили курс гирудотерапии из 10 сеансов. Всем пациентам выполнялась структурная и функциональная магнитно-резонансная томография (МРТ) с анализом статистических данных в состоянии покоя, оценивались жалобы и неврологический статус – до и после проведения курса гирудотерапии.

**Результаты исследования и их анализ.** На фоне курса гирудотерапии у пациентов с асимптомным каротидным атеросклеротическим стенозом при анализе неврологического статуса и жалоб отмечено значимое улучшение самочувствия. При проведении функциональной МРТ определены различия функциональной связанности между медиальной префронтальной корой и другими областями мозга. Отмечалась активация в основных структурах сети управляющего контроля и выявления значимости. Увеличивалась коннективность между ведущими областями головного мозга, что служит признаком улучшения его деятельности.

**Заключение.** Исследование коннективности может служить для изучения работы сетей мозга и для определения эффективности терапии. Курс гирудотерапии значимо изменял функциональную связанность областей головного мозга, изменения коррелировали с уменьшением количества жалоб. Подобная работа является пилотной и будет продолжена в целях дальнейшей разработки лечебно-профилактических стратегий с включением гирудотерапии у пациентов с высоким риском сосудистых катастроф в условиях санаторно-курортного лечения.

**Ключевые слова:** асимптомный каротидный атеросклеротический стеноз, гирудотерапия, головной мозг, коннектом, лечебно-профилактические стратегии, магнитно-резонансная томография, пациенты, функциональная коннективность

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#### Introduction

Asymptomatic carotid atherosclerotic stenosis (ACAS) is one of the causes of acute vascular episodes such as transient ischemic attack and acute stroke. It is promising to study compensatory mechanisms and functional connectivity of the brain in patients with this diagnosis. It can help to optimize the tactics of management of such patients.

At the beginning of the 21st century, a new direction in neuroscience emerged — connectomics. It is an area of research that includes mapping and analysis of the architecture of neuronal connections [1]. It has been proved that changes in the organization of neural networks (connectome) are the fundamental basis of cerebral pathology [2]. This necessitates a comprehensive study of the mechanisms of compensatory processes of the central nervous system against the background of chronic ischemia. The mechanisms of neuroplasticity underlie the compensation of impaired nervous system functions. Several mechanisms of connectome reorganization have been described which underlie neuroplasticity. Among them are changes in the specific gravity of existing connections, recombination, reconnection, and regeneration. The use of multimodal neuroimaging technique makes it possible to reveal disturbances of structural and functional neuronal connections in patients [3].

The study of neuroplasticity mechanisms in asymptomatic carotid atherosclerotic stenosis, detection of connectome changes in cerebrovascular diseases and during the treatment are topical tasks in the light of development of new preventive and therapeutic strategies, as well as prediction of disease outcomes. Hirudotherapy is a method of complementary medicine, which is widely used in the treatment of patients with vascular diseases and was proven at the pathogenetic level [4].

**The aim of the study** was to explore the state of the connectome in patients with asymptomatic carotid atherosclerotic stenosis of more than 60% when using hirudotherapy.

**Materials and methods of the study.** A single-center open uncontrolled study of resting working network status in patients with asymptomatic carotid atherosclerotic stenosis over 60% using hirudotherapy was carried out. The study adhered to the principles of good clinical practice and the Declaration of Helsinki, an extract from the protocol №17 of January 14, 2019 of the ethical committee of the V.A. Almazov National Medical Research Center with approval of the study was obtained. Written informed consent was obtained from all study participants.

The study involved 15 patients, 10 women and 5 men with asymptomatic carotid atherosclerotic stenosis of the internal carotid arteries ranging from 60-75%, the patients' age ranging from 60 to 82 years. Three patients underwent carotid endarterectomy surgery from one internal carotid artery, with persisting stenosis of more than 65% of the contralateral internal carotid artery. All patients had a history of hypertension for more than three years. Two patients had type II diabetes mellitus. The diagnosis of asymptomatic carotid stenosis was made on the basis of complaints, med-

ical history and data of instrumental examination (ultrasonic triplex examination of brachiocephalic arteries on a Logiq Q7 device (Expert General Electric).

Study exclusion criteria:

1. Psycho-organic pathology, brain tumors, epilepsy in anamnesis.

2. Severe comorbidities: acute myocardial infarction, Stage III-IV heart failure, cardiomyopathy, acute infection, etc.

3. Taking medications (barbiturates, anxiolytics, reserpine, antidepressants, narcotic analgesics), which can distort the results of therapy.

During 2 months (1-2 times a week) 10 sessions of hirudotherapy with the use of 2-5 leeches were carried out according to the patent of the Russian Federation № 2327494. Points of installation of leeches: occipital area and a zone above mastoid processes; cervical and lumbar spine, a zone of coccyx; zones of liver, spleen, heart. Against the background of complementary treatment the patients continued taking hypotensive, anti-aggregant, hypolipidemic drugs.

The patients' neurological status and complaints were evaluated before the course of treatment with hirudotherapy and 2 months after its completion.

Before and after the use of complementary methods of treatment, functional magnetic resonance imaging (MRI) was performed at rest. MP-RAGE pulse sequence — isotropic voxel  $V=0.8 \text{ mm}^3$  was used to compare functional data with brain structures. Scanning time — 9 min; 29 slices, slice thickness — 4.5 mm, number of repetitions — 120. The patients were informed about the study while awake with their eyes open. Homogeneous resting state conditions were maintained for each patient, which minimized the impact on the auditory and visual networks.

Next, magnetic resonance imaging data, in particular functional MRI at rest, were processed and the results were evaluated. For this purpose, we used the plugin CONN v.1.8 running on MATLAB (a package of applied programs), designed for determining brain connectivity and statistical establishment of active zones. Statistical analysis was performed using nonparametric McNemar criterion for dependent binary variables.

**Results of the study and their analysis.** All patients reported persistent or paroxysmal cephalgia of a throbbing/aching nature; non-systemic and/or systemic momentary, transient, or prolonged dizziness; noise in the head and and/or in the ears; hearing loss; inability to look at moving objects; flickering of flies before the eyes.

Neurological status: in 5 patients — flaccid pupillary reactions; in 4 patients — nystagmus at the extreme leads; in 3 patients — lack of convergence; in 5 patients — tremor of fingers, fingers stretched out; in 8 patients — asymmetry of tendon reflexes; in 5 patients — elements of dynamic and static-locomotor ataxia; in 7 — vegetative instability.

The patients with asymptomatic carotid atherosclerotic stenosis showed a significant improvement during the course of hirudotherapy (Table 1).

There were no worsening of the patients' condition, adverse and allergic reactions during the treatment.

After hirudotherapy treatment we observed a decrease of dynamic ataxia in 6 patients, statico-locomotor — in three of 5 patients, and autonomic instability in five of 8 patients.

Statistical two-sample t-test analysis between the groups before and after treatment revealed an increase in positive functional connectivity of the medial prefrontal cortex with the vermis and 10th zone of the right cerebellar hemisphere when the medial prefrontal cortex was chosen as the area of interest. These changes in functional connectivity correlated with clinical manifestations in the form of a decrease in the severity of vestibular disturbances. An increase in negative functional connectivity of the medial prefrontal cortex with the left middle frontal gyrus and a decrease

in the expression of negative functional connectivity of the medial prefrontal cortex with the right parahippocampal gyrus were detected.

Comparing the results obtained before and after treatment, an analysis of the data based on graph theory revealed stable connections: between the posterior parts of the middle temporal gyrus; the right anterior parts of the superior temporal gyrus; the left parts of the inferior temporal gyrus; between the visual working network, the lingual working network, the 6th zone of the right cerebellar hemisphere, the cerebellar vermis, the occipital lobe pole and a decrease in the expression of right upper and lower frontal gyrus — the lingual network (Fig. 1, 2; Table 2).

When the cerebellar network of interest is selected, a positive functional relationship with the right and left cerebellar

Таблица 1 / Table No. 1

**Оценка эффективности лечения пациентов с асимптомным каротидным атеросклеротическим стенозом, n=15**  
Evaluation of the Effectiveness of Treatment of Patients with Asymptomatic Carotid Atherosclerotic Stenosis, n=15

Симптом / Symptom	Число пациентов, чел. / Number of patients, pers.		Критерий Мак-Немара / Criterion McNemar, p
	до начала курса гирудотерапии / before a course of treatment	после курса лечения / after a course of treatment	
<b>Головная боль / Headache:</b>			
- пульсирующая / pulsating	5	0	Не применим / Not applicable
- ноющая / aching	12	3	0,008
- постоянная / constant	9	0	Не применим / Not applicable
- приступообразная и постоянная / paroxysmal and persistent	11	4	0,023
- односторонняя / one-sided	10	3	0,023
- двусторонняя / bilateral	9	2	0,023
- головная боль в целом / general headache	14	4	0,004
<b>Головокружение / Dizziness:</b>			
- несистемное / non-systemic	11	4	0,023
- системное / systemic	1	0	Не применим / Not applicable
- мгновенное, с / instantaneous, seconds	10	3	0,023
- кратковременное, мин, ч / short-term, minutes, hours	9	2	0,023
- длительное, дни, недели / long-term, days, weeks	5	0	Не применим / Not applicable
- головокружение в целом / dizziness in general	13	3	0,004
Шум в голове / Noise in my head	8	4	0,13
Шум в ушах / Noise in ears	6	3	0,25
Шум в голове и в ушах в целом / Noise in the head and in the ears in general	10	5	0,073
Снижение слуха / Hearing loss	6	5	1,0
Оптико-вестибулярный синдром / Opto-vestibular syndrome	10	2	0,013
Преходящие зрительные расстройства / Transient visual disturbances	12	3	0,008

Примечание:

1. Ухудшение не зафиксировано ни по одному из наблюдаемых показателей.
2. Улучшение составило от 16,67 до 100%, в среднем – 58,35%.
3. Статистически значимые изменения состояния наблюдались по следующим показателям – ноющая, приступообразная и ноющая, односторонняя, двусторонняя головная боль в целом; головная боль в целом; мгновенное, кратковременное головокружение и головокружение в целом; оптико-вестибулярный синдром и преходящие зрительные расстройства.
4. Улучшение в 100% случаев было достигнуто по следующим показателям: пульсирующая, постоянная головная боль; системное, системное в сочетании с несистемным, длительное головокружение

Note:

1. No deterioration was recorded in any of the observed indicators.
2. The improvement ranged from 16.67% to 100%, on average - 58.35%.
3. Statistically significant changes in the state were observed in the following indicators - aching, paroxysmal and aching, unilateral, bilateral, and in general headache; non-systemic, instantaneous, short-term and in general dizziness; opto-vestibular syndrome and transient visual disorders.
4. Improvement in 100% of cases was achieved in the following indicators: throbbing, persistent headache; systemic, systemic in combination with non-systemic, prolonged dizziness

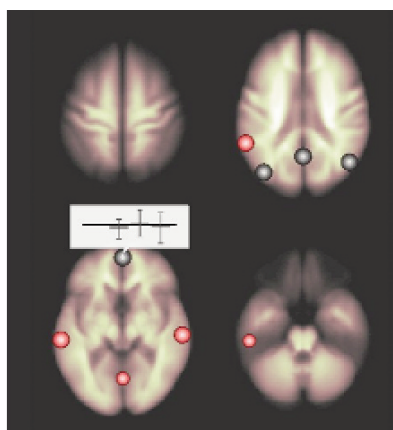
hemispheres (8 zones), cerebellar vermis, posterior cingulate and angular gyrus areas is determined (Fig. 3).

Discussion. According to the results of the present study, after a course of hirudotherapy in patients there was a statistically significant decrease in the frequency of dizziness, cephalgia, noise in the head and ears. Similar positive dynamics was earlier noted by us and a number of other authors in patients with hypertensive angioencephalopathy and chronic vertebral-basilar insufficiency [5]. Decrease of expression of visual impairments at application of hirudotherapy is proved by ophthalmologists. In the Interdisciplinary Scientific-Technical Complex "Eye Microsurgery"

hirudotherapy is used for about 20 years, more than 300 patients annually receive hirudotherapy courses [6].

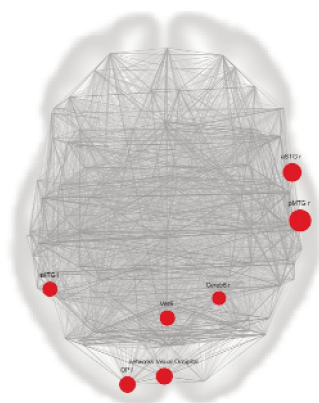
The study of functional MRI data at rest determined the activation of the main structures of the control network and revealing significance after hirudotherapy application. Clinically there was an attenuation of vestibular disorders, which was manifested by an increase of functional connectivity of the medial prefrontal cortex by the cerebellum. The weakened connectivity with the left medial frontal gyrus may indicate a decrease in the inhibitory component of the network.

According to some studies, patients with chronic cerebral circulatory disorder showed a loss of inter- and intrahemi-



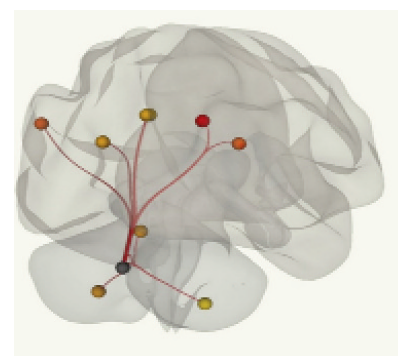
**Рис. 1.** Результаты внутригруппового сравнения до и после курса гирудотерапии – красным отмечены участки, которые связаны с МПФК положительно, синим – отрицательно

**Fig. 1.** Results of intragroup comparison before and after the course of hirudotherapy – red marked areas that are associated with MPFC positively, blue - negatively



**Рис. 2.** Картированные данные функциональной связности после курса гирудотерапии – красным отмечено усиление функциональной связности

**Fig. 2.** Mapped data of functional connectivity after a course of hirudotherapy – red indicates an increase in functional connectivity



**Рис. 3.** Мозжечковая сеть: межгрупповое сравнение

**Fig. 3.** Cerebellar network: intergroup comparison

Таблица 2/Table No. 2

**Выраженность функциональных активаций: межгрупповое сравнение**

Expression of functional activations: intergroup comparison

ROI*	T**
Network	-0,98
Cerebr	1,85
toITG l	1,98
pMTG r	2,95
aSTG r	2,48
Visual Occipital	2,24
OPI	2,19
Vermis 6	2,03

\* ROI –зона интереса / area of interest

\*\*T –коэффициент Стьюдента / Student's coefficient

spheric connectivity between network structures and managing control and relevance detection, which is a disconnection phenomenon [7, 8]. After treatment with the use of complementary methods, the connectivity of the leading structures of the brain increased, which may be a sign of changes in brain functioning in the form of restoration of emotional and behavioral disorders and cognitive impairment in patients with asymptomatic carotid atherosclerotic stenosis.

**Conclusion**

The available evidence of pathogenetic effects of hirudotherapy inducing a complex of reactions aimed at the sequential elimination of ischemia and hypoxia and microcirculatory disorders was reflected in significant changes of the connectome in patients with asymptomatic carotid atherosclerotic stenosis, which correlated with a reduction of complaints. This work can be considered pilot; continuation of the research will give an opportunity to converge the methodological apparatus of evidence-based medicine with such effective and well-proven method of complementary medicine as hirudotherapy.

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