Functional Connectivity Assessment in Patients with Chronic-type Tension Headaches after Applying Osteopathic Correction

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Abstract: Clinical and neuroimaging comparison of the dynamics of changes in the pain connectome against the background of osteopathic correction in patients with chronic tension-type headaches. We examined 24 patients with chronic tension type headaches, aged 24 to 43 years. Patients underwent resting-state functional MRI before and after first osteopathic manipulation. Complaints were evaluated and patients were surveyed to assess the intensity of headache and its impact on different areas of life, quality of life, situational and personal anxiety before and after therapy. Changes in the functional connectivity of the in patients with tension headaches after osteopathic manipulation were found to correlate with a positive clinical picture. Changes in the functional connections of the medial prefrontal cortex with other areas of the brain were detected in patients with chronic tension-type headaches when using a single osteopathic correction. There was an improvement in the condition of patients both in the subjective assessment of complaints and in the objective assessment of their condition on scales. The use of methods for statistical analysis of neuroimaging data, in particular resting-state functiontional MRI, made it possible to see the differences objectively by mapping different colors using color scales, which greatly simplifies the entire analytical process. Clinical and neuroimaging comparison of the dynamics of changes in the pain connectome against the background of osteopathic correction in patients with chronic tension-type headaches provides potentially new approaches to the diagnosis and treatment of pain syndrome.

ABBREVIATIONS

DMN – default mode nerwork
CTTH – chronic tension-type headache
FC – functional connectivity
MPFC – medial prefrontal cortex
TTH – tension-type headache

1 INTRODUCTION

Among all types of headaches, the leading role belongs to tension-type headache (TTH), the prevalence of which among the population is up to 45-64%, while chronic tension-type headache (CTTH) accounts for 1,7–4% (Mathew, 2006; Jensen, 2008). CTTH is a serious medical and social problem that leads to a decrease in the working capacity and quality of life of patients. It is proved that the etiopathogenesis of TTH involves extensive neural networks that can extend beyond the somatosensory system (central divisions) (Filatova, 2020). It should be noted that in the treatment of tension-type headaches, there is an excessive use of medications. That is why the approach based on non-drug methods of influence seems to be relevant.

One of the promising methods of non-drug correction of tension headaches is osteopathic correction. There are studies that show a decrease in

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pain sensitivity and pain intensity after treatment using osteopathic techniques (Bredikhin, 2015; Miroshnichenko, 2017).

One of the serious problems of modern Algology is the objectification of pain intensity and the effectiveness of analgesic treatment. In addition to subjective assessment using pain scales with low validity, attempts are being made to develop methods for objectively measuring the intensity of tension headaches during treatment – by determining the concentration of serotonin in the blood plasma of patients or by studying the latency of P300, but these approaches are difficult to reproduce and also have low validity (Rachin, 2005). The most objective and valid analysis of connections between different areas of the brain and the assessment of neural networks is possible using resting-state functional MRI, which is used to evaluate the effectiveness of evidence-based medicine methods.

Currently, the issue is devoted to the study of neuroplasticity in patients with CTTH during the use of osteopathic correction, and objectively proved the effectiveness of this method remains poorly understood. Determining changes in functional relationships is promising in forming a new view of the etiology and pathogenesis of CTTH and makes it possible to develop effective tactics for treating patients (Patil,2017; Jutzeler, 2015; Baliki 2014, Lepekhina, 2020).

2 PURPOSE

Connectome study in patients with chronic-type tension headaches with the use of osteopathic correction.

3 MATERIALS AND METHODS

3.1 Study Population

An open, single-center, uncontrolled study of the connectome condition was conducted in patients with tension headaches during a course of treatment with osteopathic methods.

We observed 24 patients (aged from 24 to 43 years, age - 33±0.5 years) with CTTH, duration of the disease from 1 year to 18 years (duration - 4.4±0.7 g). Other causes of headache were excluded.

The diagnosis of CTTH was based on anamnesis and complaints. All patients complained of paroxysmal and / or persistent headaches of one - or two-sided localization of aching (41%), pulsating character of weak (23%) and moderate intensity (36%). Headaches were more often of two-sided localization, were of a pressing/compressing/ non-pulsating nature, lasting from 60 minutes to several days, of mild or moderate intensity, which did not increase with normal physical activity, and were not accompanied by nausea and vomiting. Patients reported headache more than 15 days a month, for the last 6 months. The study was approved by the ethics committee of the Federal State Budgetary Institution «National Medical Research Center n.a. V.A. Almazova» of the Ministry of Health of Russia (extract from the protocol No. 41 of 02/12/2018).

Criteria for exclusion of patients from the study were: 1. The presence of a history of psycho-organic pathology, epilepsy, brain tumors, injuries of the brain and spinal cord. 2. The presence of severe concomitant pathology (exacerbation of rheumatism, acute infections, cirrhosis, alcoholism, drug addiction, cardiomyopathy with thromboembolism in the arteries of the brain, acute myocardial infarction, heart failure 3-4 severity, blood diseases). 3. The simultaneous administration of drugs that can distort the results of treatment (anxiolytics, antidepressants, barbiturates, lithium preparations, narcotic analgesics, reserpine).

3.2 MR Imaging Protocol

All patients underwent structural MRI with obtaining T1 and T2 weighted images and FLAIR (Fluid attenuated inversion) to exclude brain tumors, strokes and other pronounced pathological changes. All patients underwent functional resting state MRI at 3 time points – before and after 10 minutes after applying the first osteopathic technique. Pulse sequence data of a T1-weighted gradient echo (MP-RAGE – Magnetization Prepared Rapid Acquired Gradient Echoes) was collected to combine fMRI data with anatomical structures of the brain, slice thickness – 4.5 mm, number of slices – 29, the number of repetitions – 120, scan time – 6 minutes. The main feature of this sequence is its high resolution and 0.8 mm isotropic voxel. BOLD (Blood Oxygenation Level Dependent) were using with repetition time (TR) = 3000 ms, echo time (TE) = 50 ms, field of view (FOV) = 230 mm and matrix size 128*128, slice thickness – 4.0 mm, the number of repetitions – 120, scan time – 6 minutes.

3.3 Image Analyses

Analyzing the data of functional MRI, when performing an intergroup statistical analysis (two-sample t-test, comparing the resting state before treatment and after osteopathic correction) with the choice of the medial prefrontal cortex (MPFC) as the region of interest.

3.4 Statistical Analyses

For statistical analysis, the non-parametric McNemar test for dependent binary indicators was used. Statistical processing and evaluation of the results of neuroimaging studies of each patient individually, as well as their group totality (resting state fMRI data) were carried out using the CONN v.18 software package (Functional connectivity toolbox), designed to determine the relationships between different parts of the brain, statistical mapping of activation zones, determining the structure of various resting state networks and functional networks of the brain.

3.5 Results

According to the results of the study, after the use of osteopathic manipulations according to resting-state fMRI data, changes in the functional connectivity (FC) were observed. When performing osteopathic correction, there is a functional reorganization of neural networks involving, first of all, of default mode network (DMN). The choice of the medial prefrontal cortex (MPFC) as a region of interest in the study is due to its importance as one of the central links in the DMN.

When selecting the MPFC as the region of interest in the right hemisphere, the positive functional connection with the right parahippocampal gyrus was determined to be enhanced. In the left hemisphere, there was an increase in the positive FC with the putamen and a decrease in the negative FC with the upper left parietal region.

Functional MRI data were obtained when comparing the state at rest before and immediately after 10 minutes following osteopathic manipulation: when performing an intergroup statistical analysis ($p<0.005$) (two-sample t-test, seed-to-voxel), the result of an intergroup comparison is presented, which demonstrates changes in activity (table 1).

Table 1: The degree of activations severity before and after 10 minutes following osteopathic manipulation. Region of interest - the medial prefrontal cortex.

ROI	Statistical indicator, T
The upper parietal region, left	-3.13
Parahippocampal gyrus, right	2.43
Putamen	-2.16

Schematic representation of data from the intergroup analysis: shows how MPFC is related to other areas of the study, where more pronounced activity is observed in the parahippocampal gyrus, and a decrease in activity in the upper parietal region and the putamen (Fig. 1).

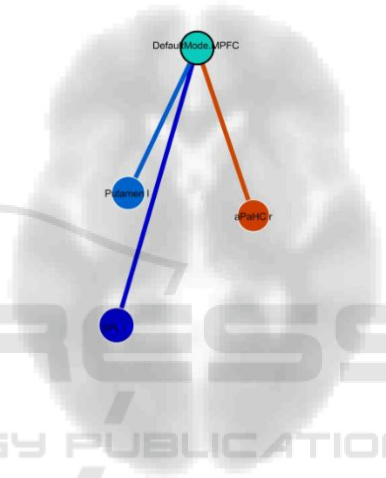

Figure 1: The results of the intergroup analysis of resting-state functional MRI, before and after 10 minutes following osteopathic manipulation. Schematic data.

For the most convenient visualization, we combined fMRI data with anatomical structures of the brain T1-weighted gradient echo MP-RAGE (Magnetization Prepared Rapid Acquired Gradient Echoes-gradient echo with magnetization preparation and rapid data collection) (Fig. 2, 3). When selecting the MPFC as the zone of interest in the right hemisphere, the positive FC with the right parahippocampal gyrus was determined to be enhanced. In the left hemisphere, there was an increase in the positive FC with the putamen and a decrease in the negative FC with the upper left parietal region.

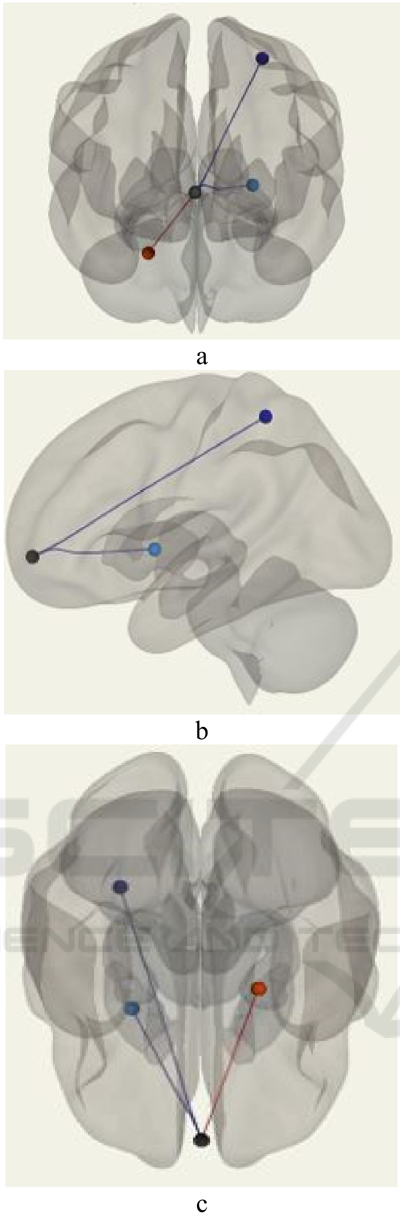

Figure 2: (a - axial, b - sagittal, c - coronal). The results of the inter-group analysis of the resting-state functional MRI (roi-to-roi). 3-D reconstruction. Region of interest: MPFC. The red color indicates a positive FC, and the blue color indicates a negative FC.

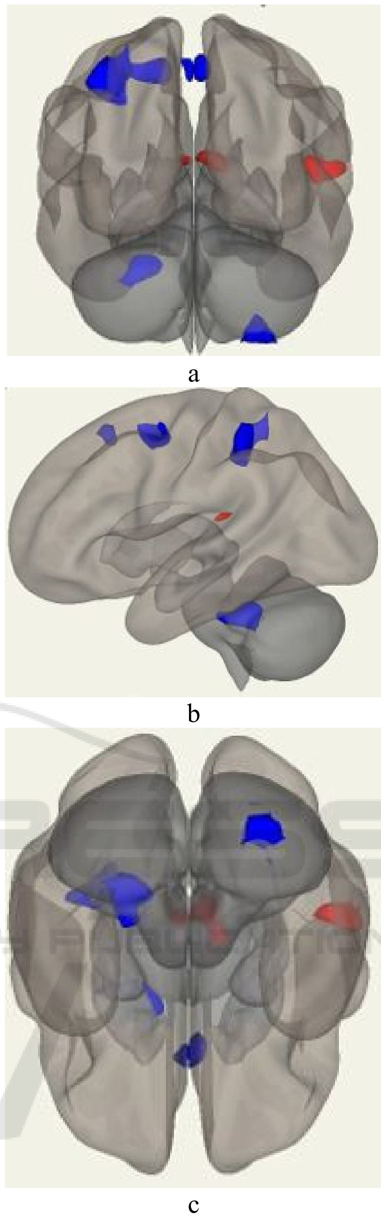

Figure 3: (a - axial, b - sagittal, c - coronal). The results of the inter-group analysis of the resting-state functional MRI (seed-to-voxel). 3-D reconstruction. Region of interest: MPFC. The red color indicates a positive FC, and the blue color indicates a negative FC.

The study was the first to identify changes in the FC of the brain after a single procedure of osteopathic correction in patients with CTTH. The use of methods for statistical analysis of neuroimaging data, in particular resting-state fMRI, made it possible to see the differences objectively by mapping different colors, which greatly simplified the entire analytical process.

There were no adverse reactions due to osteopathic correction, as well as deterioration of the condition of patients with CTTH during the treatment.

The possibilities of modern visualization methods expand the understanding of the mechanisms of neurological diseases by studying connectome of the brain. Using resting-state fMRI allows you to objectively assess neuronal activity and study changes in CTTH.

When performing osteopathic manipulations, the functional reorganization of neural networks occurs with the involvement of the network of the DMN. The study examined changes in the FC of the medial prefrontal cortex with other parts of the brain. The choice of the medial prefrontal cortex as a region of interest in the study is due to its importance as one of the central links in the DMN. The MPFC connects large areas that include the orbitofrontal cortex and structures such as the central gray matter of the midbrain, amygdala, and hypothalamus, while playing an important connecting role in transmitting somatosensory information to structures that are responsible for motor and visceral responses, participating in the internal reward system and responsible for decision-making. According to recent data, the parahippocampal gyrus is an intermediate link in the DMN, which connects the MPFC with the limbic system, and participates in the processes of the internal reward and memory system (Ward, 2014). The increase in the positive FC of MPFC with the parahippocampal gyrus in the right hemisphere in patients with CTTH after performing osteopathic manipulation revealed in our study may indicate activation of the functional pathway associated with a positive emotional response in the reward system.

In the left hemisphere, there was a weakening of the negative FC with the upper left parietal region and an increase in the positive FC with the putamen. The upper parietal cortex is part of the vast preclinical zone, which, along with the MPFC, is one of the important links in the DMN, which are involved in the processing of sensory-motor signals and attention. Changes in the FC between the upper parietal region and the MPFC may indicate a decrease in activity in this area DMN. The putamen is a subcortical structure that belongs to the significance determination network, and the strengthening of links between this area and the MPFC may indicate activation of DMN.

So, changes in the FC of the MPFC with other areas of the brain were detected when applying a single osteopathic correction in patients with CTTH.

4 CONCLUSIONS

To date, the number of full-fledged studies on changes in the FC of the brain in patients with CTTH is limited, which makes this area even more relevant.

The current study showed the importance of evaluating the FC that ensure the interaction of brain structures. Changes in the FC of the DMN were identified in patients with CTTH after the use of osteopathic correction, which require further study. The results of the study of FC of the brain in patients with CTTH expand the understanding of the pathogenesis of this type of headache and improve the treatment regimens used in patients.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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