Investigation of the Neuro-electrostimulation Mechanisms by Means of the Functional MRI: Case Study

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Abstract: The article overviewed contemporary neuromodulation approaches and challenges. The importance of the neurostimulation techniques was justified. The SYMPATHOCOR-01 neuro-electrostimulation device characterization was presented. The case study of the neuro-electrostimulation mechanisms by means of the neuroimaging was described. Case study consisted of 3 phases: imaging prior to the neuro-electrostimulation procedure, imaging right after the neuro-electrostimulation procedure and imaging after a 5-day stimulation course. Results of the functional magnetic resonance imaging revealed improvement of the functional connectivity strength in several brain regions as well as normalization of default mode network activity.

1 INTRODUCTION

The relevance of new efficient methods development for the central nervous system (CNS) organic damages treatment is defined by the spread of these diseases, aging of population, growth of stress and technogenic factors (Zuliani *et al.* 2012). To some extent, a barrier in the development is lack of knowledge about the pathophysiological models of the functional disorders in the human brain. It justifies the necessity of contemporary methods attraction for the investigation.

One of the most rapidly developing directions in this sphere is the neuromodulation (Thin *et al.* 2013). However, the contemporary developments of the neuro-electrostimulators, applied in the medical practice, faces the high complexity of the nervous system organization, including powerful mechanisms of the adaptation to the external field's influence.

2 NEUROMODULATION APPROACHES

At the moment, basic approach for the treatment of central and peripheral nervous systems' disorders is the so-called neuroprotective therapy (Stocchi and Olanow 2013). On the one hand, it improves normalization and enhance physiological activity of the neural tissue. On the other hand, it leads to recovery of structural damage, caused by various pathogenic effects, including traumatic, infectious-inflammatory, vascular, and degenerative effects.

2.1 Physiological Mechanisms of the Neural Adaptation

Generally, damage of the nervous systems, involves whole complex of chains in the pathological process. Clinically, it leads to numerous neurological, mental, autonomic and regulatory disorders. Often it requires application of not a single 'universal' drug, but a complex therapy of the different medicines.

The situation becomes unfavorable, as simultaneous usage of many drugs, accumulates not

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only treatment effects, but also the side effects, which results from polypharmacy. In case of polypharmacy, the side effects suppress therapeutic effects, and the treatment becomes ineffective and dangerous (Maher *et al.* 2014).

Described situation is especially unfavorable in cases when treatment interferes with the natural regulatory and adaptive process of the CNS, essentially acting as the stress-factor. In this case, stress adaptation systems take up work. These systems represent sophisticated regulatory complex, which is crucial for the activation and coordination of all changes in the organisms as response to the stress.

Through both, self-regulation process and external regulation the stress system is implemented. The self-regulation of the stress system is based on feedback principles: adrenocorticotropic hormone (ACTH), cortisol and brain structures are fundamental (Jovanovic *et al.* 2010). Mechanisms of the external regulation are implemented by the stress-limiting system, which constrains stress system activity and excessive stress-reaction on central and periphery scale. Central scale includes GABAergic, opioidergic and serotoninergic systems; whereas the periphery scale includes adenosine, prostaglandins and antioxidant system, as well as the *NO* generation system (Stahl and Wise 2008). Moreover, the endogenic neuropeptids, like substance *P*, Brain-derived neurotrophic factor (BDNF) and others, are also important for the stress reaction regulation. (Dupont *et al.* 1981, Rothman *et al.* 2012). At the same time, complex neurohumoral mechanisms of the stress-realizing and stress-limiting interaction, organize multiphasic adaptation reaction of the organism (Holaday 1983, Knapman *et al.* 2012).

Furthermore, in case of a stress, caused by the disease, by the direct and side-effects of the drugs, complicated mechanisms of immune system disorders are implemented. Immune system disorder may result in the secondary immunodeficiency state of the neurogenic origin (Turnbull and Rivier 1999, Kronfol and Remick 2000, Davis *et al.* 2008).

If one improves the adaptive possibilities of autonomic regulation, then central regulation mechanisms come to help. Central regulation mechanisms include direct control of endocrine, immune, cardiovascular and digestive systems, by means of the comprehensive communication networks of neurohumoral interaction, hormones, neuromediators and immunotoxic agents (Dedovic *et al.* 2009).

2.2 Therapeutic Techniques

There is a tendency to assume, that the basis of the neuro-protective therapy are numerous medicines, which have wide range of action mechanisms and pharmacokinetic properties. Different medicines affect on range of the pathogenetic components of the particular pathologic process (Greenberg *et al.* 2009).

However, the pharmacological approach is effective only among the one third of the patients. In most cases, the life-long drug regimen is implied, which is accompanied by the quantity side effects. Essentially, the pharmacological approach is just a substitution therapy and does not treat the disorder itself (Stahl and Moore 2013).

2.3 Neuro-electrostimulation Techniques

During recent years, a number of investigations have intensified for the universal and less harmful neuroprotection techniques. Such techniques were labeled as neurostimulation (Charleston *et al.* 2010). To the date numerous data on specific neurostimulation techniques application have been accumulated. A number of such key features can classify such techniques:

- exposure area – brain, spinal cord, periphery nerves;
- invasive and non-invasive techniques;
- physiological properties of stimulated neural structures - afferent and efferent stimulation;
- mechanism of the stimulation – internal and external stimulation;
- the size of stimulated neural tissues – local and general stimulation;
- physical nature of the stimulating factor – magnetic, electric, ultrasound, optic stimulation.

One can obtain different clinical effects of the neurostimulation depending on the stimulated department of the nervous system. In either case, the nervous system performs the integral function and provide interconnected regulation of whole organism systems activities. It means that neurostimulation effects are not limited by the nervous system itself, but also can influence the variety of processes in the organism as a whole.

Contrary to the complex medicines therapy, proper application of the physical neurostimulation does not cause additional stress reactions of the organism, as it does not actively interfere in

regulatory, biochemical and immune process of the organism. This fact allows widely applying neurostimulation techniques for the medical rehabilitation in many pathological cases.

It is of great interest to find new targets and technical means of neurostimulation, based on the anatomical knowledge and knowledge of the nervous system physiology, for the particular medical tasks.

2.4 SYMPATHOCOR-01 Device

The SYMPATHOCOR-01 device implements the technology of multi-channel neuro-electrostimulation. Spatially distributed physical field is formed: its features are in accordance with endogenic process in the neural structures. This technology allows managing activity of the conducting formations and performs the neuromodulation process. The medical application of the SYMPATHOCOR-01 device is implemented as the DCASNS technique - Dynamic Correction of the Sympathetic Nervous System Activity. The DCASNS technique provides correction of autonomic balance, defined by the relation between the activities of the parasympathetic and sympathetic departments of the autonomic nervous system (ANS) (Kublanov, Shmirev, *et al.* 2010).

At present, the SYMPATHOCOR-01 device is applied in the clinical practice to correct and control the following pathologies: migraine, neurocirculatory dystonia, traumatic brain injury and brain concussion, alcohol and narcotic abstinences, hypertonic diseases, obliterate atherosclerosis of the lower limbs, Raynaud's disease, trigeminal nerve inflammation, sensorineural deafness, degenerative diseases of vision and atrophy of the optical nerve, osteochondrosis of the back bone, neuropathies of various genesis, cephalalgia syndrome, hyperhidrosis syndrome, syndrome of the orthostatic hyposthenia and postural tachycardia, vestibular disease, vegetative deregulation syndrome, epilepsy (Kublanov *et al.* 2017).

The design process of the SYMPATHOCOR-01 device medical application was accomponied by the experimental studies on laboratory animals by modelling the chronical pathological (muscle ischemia) and the actute (immobilising stress) states (Kublanov, Danilova, et al. 2010, Kublanov et al. 2012).

For pathological state, in the previous works was noted that on organs and tissue level the blood supply recovery is associated with increase in the number of the capillaries. On the cross-section of the muscle, after the neuro-electrostimulation application, the swelling, which is characteristic for the ischemia case, was also decreased. Moreover, the visually noted recovery of the transverse striation, define the regeneration of the muscle tissues. On the cellular level, the decrease of the permeability of the damaged membranes is noted. On the molecular level, the endogenic toxins number was reduced.

For the acute state, after a single procedure of the neuro-electrostimulation, the motion activity had a tendency towards the normalization. On the cell level, the increased membranes permeability of the cells and muscle fibers did not worsen. On the organism level, the behavior reaction changed: the adaptation to the immobilized stress was improved and the animal became less aggressive.

The single-photon emission computed tomography images have shown that the neuro-electrostimulation by the 'SYMPATHOCOR-01' device allows to change neurogenic regulation of the vascular tone, to improve neurometabolism in the brain, to suppress epileptic activity, stimulating neurotransmission, to recover intracerebral connections (Kublanov et al. 2004).

Emergence of the modern neurovisualization methods opens the possibilities in the neuroplasticity investigation. In particular, functional magnetic resonance imaging (fMRI), which is an intravital non-invasive dynamic investigation of active brain structures during their functioning. The fMRI method is based on different properties of oxyhemoglobin, carrier of O_2, and deoxyhemoglobin, a product formed in the brain parenchyma in magnetic field. This proportion is reflected by the BOLD-phenomenon (blood oxygenation level independent), a marker of neuronal activity. Stereotyped or, on the contrary, heuristic actions as well as sensorimotor, visual-auditory, and speech operations are associated with the formation and/or reorganization of preexisting neuronal ensembles (NE) in the brain. Their activity, being spontaneous or produced by the environment, appears as an increase of local blood filling of the brain tissue and in modulation of the mechanisms of blood flow rate and volume regulation in the brain (Savostyanov *et al.* 2016).

The goal of the current pilot study is to investigate the influence of the SYMPATHOCOR-01 stimulation by means of the functional neurovisualisation.

3 CLINICAL CASE STUDY

In the December of 2016, at the State Scientific-Research Institute of Physiology & Basic Medicine, the pilot study of the hemodynamic reactions, caused by the neuronal activity of the brain, by means of the fMRI, was conducted.

Single male patient K., age 25, diagnosed with ICD T90.5 (Sequelae of intracranial injury), has participated in the pilot study. The patient K. has signed the informative participation consent. The study was carried out on the MR system GE Discovery MR750W, 3.0 Tesla, in accordance with the following protocols:

1) T1 SPGR 3D reconstruction, up to 256 cross-sections, voxel size 1 mm3; mandatory capturing the whole head surface, including nose and ears;
2) fMRI in the resting state mode, and in visual stimuli presentation mode (33 cross-sections, thickness up to 4,5 mm)
3) tractography (diffusion tensor imaging - DTI, 72 cross-sections, 2 mm each; 64 directions)
4) T2-WI, FLAIR (weighted images for exclusion of the chronic gliosis sources). The stimuli were send by means of the Nordic NeuroLab BrainEx.

For registration to standard space a T1 high-resolution 3D MPRAGE (magnetization prepared rapid gradient echo) was performed. with the following scan parameters: repetition time (TR)=2.5 s, echo time (TE)=3.52 ms, 190 sagittal slices with no gap, field-of-view (FoV)=230 mm, flip angle (FA)=8°, in-plane resolution=1.2×1.2 mm2, slice thickness=1.2 mm. During RS-fMRI acquisition, using gradient echo T2* weighted EPI, participant was instructed to keep the eyes closed and not to think about anything. The imaging parameters were: 100 volumes, TR=3 s, TE=52 ms, FA=90°, 28 interleaved slices, slice thickness=5 mm, imaging matrix 64×64 and FoV=220 mm.

The study timeline is presented in the table 1.

Table 1: Study timeline.

I phase	II phase	III phase
-T1-sag -RS -Visual Nordic -DTI -MRA	-T1-sag -Visual Nordic -DTI -MRA	-T1-sag -RS -Visual Nordic -DTI -MRA

Here:
T1-sag – weighted image in the sagittal projection; RS - resting state functional MRI (BOLD signal); Visual Nordic – functional MRI in the visual stimuli paradigm (activation of the visual cortical areas); MRA - MR-angiography, a medical test that helps physicians diagnose and treat medical conditions and diseases of the blood vessels.

The first phase was conducted for the baseline state evaluation. The second phase was conducted immediately after the neuro-electostimulation procedure in order to evaluate short-term reaction of the CNS. The third phase was conducted 3 days after 5 procedures of the DCASNS in order to evaluate long term reaction of the CNS. The biotropic field features of the SYMPATHOCOR-01 were set in accordance with the DCASNS technique. There were two 30-minutes procedure every day.

Data were analysed using Matlab (SPM12, CONN14). For a ROI-based analysis, Medial Prefrontal Cortex was chosen as a seed ROI, as it is considered a part of default mode network (DMN).

4 RESULTS

The one-sample t-test showed spatial pattern of activation (connectivity) and deactivation in DMN. In I and II phases along decreased functional connectivity in DMN, following changes were identified:

- increased negative functional connectivity strength (FCs) with Anterior and Dorsolateral Prefrontal Cortex (BA9, BA46),
- decreased positive FCs with Ventral Posterior Cingulate Cortex (BA31), Premotor (BA6) and Somatosensory Cortex (BA7).

In phase III positive FCs with Angular Gyrus (BA39), Dorsal Posterior Cingulate Cortex (BA 31), Dorsal Frontal Cortex (BA8), Associative Visual Cortex (BA19), Orbitofrontal Cortex (BA11), Inferior Prefrontal Gyrus (BA47) appeared stronger. Although less areas of deactivation were present. Besides, the whole DMN activity showed symmetry. In phase II a slight increase in overall activation strength was noted.

The participant suffered periodic headaches of a pressing nature without a clear localization, provoked by increased physical and emotional stress, as well as excessive sleep, and episodic tension headaches. With that in mind, we can outline, that, regarding DMN activity, stress induced functional connectivity alterations took place initially in the medial prefrontal cortex, medial orbitofrontal cortex, posterior cingulate cortex and some other regions. The follow-up examination showed definite normalization of DMN activity.

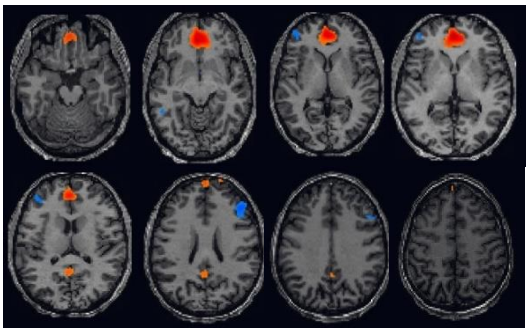

Figure 1: I phase – prior to the treatment.

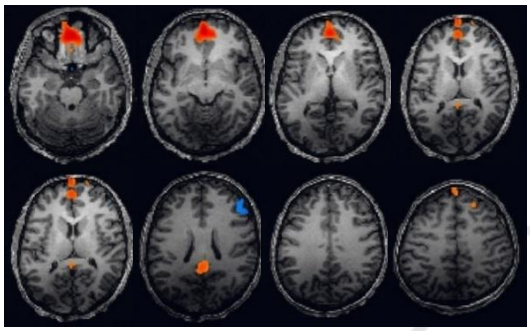

Figure 2: II phase – after a single DCASNS procedure.

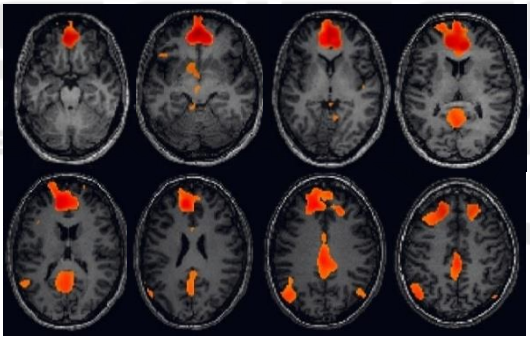

Figure 3: III phase – after 5 DCASNS procedures.

5 CONCLUSIONS

Results of the SYMPATHOCOR-01 neuro-electrostimulation effects by means of the functional neuroimaging allowed revealing areas of the most active changes in the brain tissues. One can claim that effect of the SYMPATHOCOR-01 device is spreading from the neck area through the afferent conducting paths up to the cortical formations of the brain.

Obtained in the pilot study data allows to consider the fMRI technology as the promising tool for the neuro-electrostimulation mechanisms investigation. The data could also form new treatment techniques of the non-invasive multi-electrode neck neural structures electrosimulation application for treatment of the psychiatric and neurological disorders. Namely, disorders accompanied by the neurodeheneration (Alzheimer disease, Parkinson disease, dementias); consequences of the brain traumas, neurotoxications, depressive and anxiety disorders, strokes.

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