Recovery of the Cognitive Function by the Non-Invasive Multichannel Neuro-Electrostimulation for Patients with Amnesic Syndrome

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Abstract: The efficiency of non-invasive multichannel neuro-electrostimulation device for recovery of cognitive functions is presented in article. The article contain description of the structural schematic and algorithm of the microcontroller execution program of "SYMPATHOCOR-01" device. The possibility of the "SYMPATHOCOR-01" application for the cognitive disorders treatment is justified. As the example, results are presented that involved five middle-aged men with signs of pronounced organic amnesic syndrome, previously held specialized treatment in hospital. As a result, the stimulation rate during the three weeks of recovery could achieve stable fixing of memory and other cognitive functions in all the patients according to clinical observation and methods of neuropsychological assessments FAB, MoCA and MMSE. A significant positive trend noted by the results of the data analysis of EEG and heart rate variability. A hypothesis mechanism for clinical effect is formulated.

1 INTRODUCTION

Nowadays, population ageing, more complex technosphere and rapid growth of social stressors define importance of cognitive disorders, caused by organic injuries of the Central nervous system (CNS). The memory is one of the most important cognitive function. Severe disorders of memory are observed for patients with organic amnesic syndrome. The amnesic syndrome arises as a result of the severe cerebral injury or the intoxication of the brain (Kopelman, 2002). Neuromodulation, which is a technology shown to induce neuroplasticity changes, is the alternative to the traditional pharmacological methods of the cognitive function recovery (Doidge, 2010). However, contemporary elaborations of the neuro-electrostimulators applicable to this task in medicine have a number of the significant drawback that reduce efficiency of the exposure. For example, the quick adaptation of the nervous system to exposure to the external electric fields results in a decreased reaction when the exposure is continuous.

2 SYMPATHOCOR-01 DEVICE

Group of scientists and engineers from the Ural Federal University developed the "SYMPATHOCOR-01" device. The device is included in the register of medical equipment products of the Russian Federation (registration certificate № FCR 2007/00757) and has the Certificate of correspondence to the requirements of the regulations GOST R 50444-92. Block diagram of the "SYMPATHOCOR-01" device is shown in Fig. 1. The device includes neuro-electrostimulation subsystem, electrocardiogram (ECG) registration subsystem, microcontroller and a control unit.

Neuro-electrostimulation subsystem is used to create spatially distributed field of current impulses, which allows correcting the ANS activity. ECG registration subsystem is used for ECG registration in the first limb lead scheme for the consequent ECG analysis, heart rate variability acquisition and decision making for the structural changes of the neuro-electrostimulation field. Microcontroller is

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used to receive and to process commands from the control unit, neuro-electrostimulation subsystem and the ECG registration subsystem, and to coordinate subsystems.

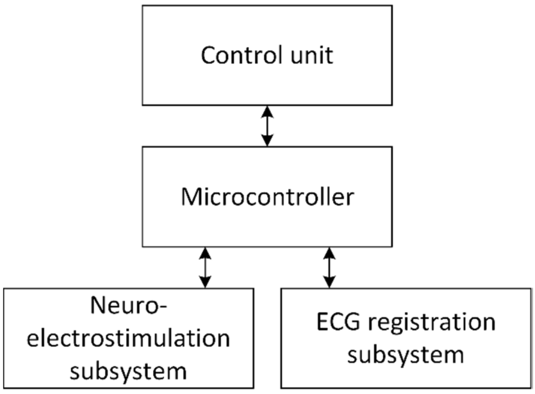

Figure 1: Block diagram of the neuro-electrostimulation device.

In order to display information about current neuro-electrostimulation device state, microcontroller cyclically poll the neuro-electrostimulation subsystem and ECG registration subsystem, pack information about these subsystem states into information messages and transmit packets to the control unit. Current ECG data, received from the ECG registration subsystem are buffered, packed into information messages and transmitted to the control unit for the further processing.

The control unit is used by the doctor to control neuro-electrostimulation procedure, to process and to analyze ECG signal, to alter neuro-electrostimuilation field of current impulses characteristics, depending on neuro-electrostimulation program and results of the ECG signal analysis. A personal computer or a mobile device can be used as the control unit.

The "SYMPATHOCOR-01" device implemented as a mobile unit and has dimensions of 90.0 x 50.0 x 18.5 mm. The "SYMPATHOCOR-01" device general view is shown in Fig. 2. The "SYMPATHOCOR-01" device main printed circuit board is shown in Fig. 3.

Neuro-electrostimulation susbsystem consists of:

- two multi-element electrodes, first performs anodes function, and second – cathodes function
- voltage controlled current source (VCCS)
- anodes multiplexer, which connects one of the partial anodes to the positive pole of VCCS
- cathodes multiplexer, which connects one of the partial cathodes to the negative pole of VCCS

Figure 2: The "SYMPATHOCOR-01" device view.

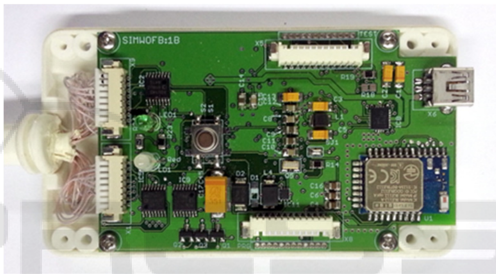

Figure 3: The "SYMPATHOCOR-01" device main printed circuit board view.

During neuro-electrostimulation procedure, microcontroller executes program implemented in accordance with the algorithm, that shown in Fig. 4.

Alteration of the neuro-electrostimulation field of current impulses state is possible only at discrete time points. These discrete time points are determined by the formula:

$$t = a * T + n * \tau, \tag{1}$$

where $a \in N$, N – set of all natural numbers, T – impulses "packets" repeat interval,

$$n \in N, 0 \le n \le K, \tag{2}$$

where K – number of partial cathodes, involved in neuro-electrstimulation procedure, τ – duration of the partial impulses.

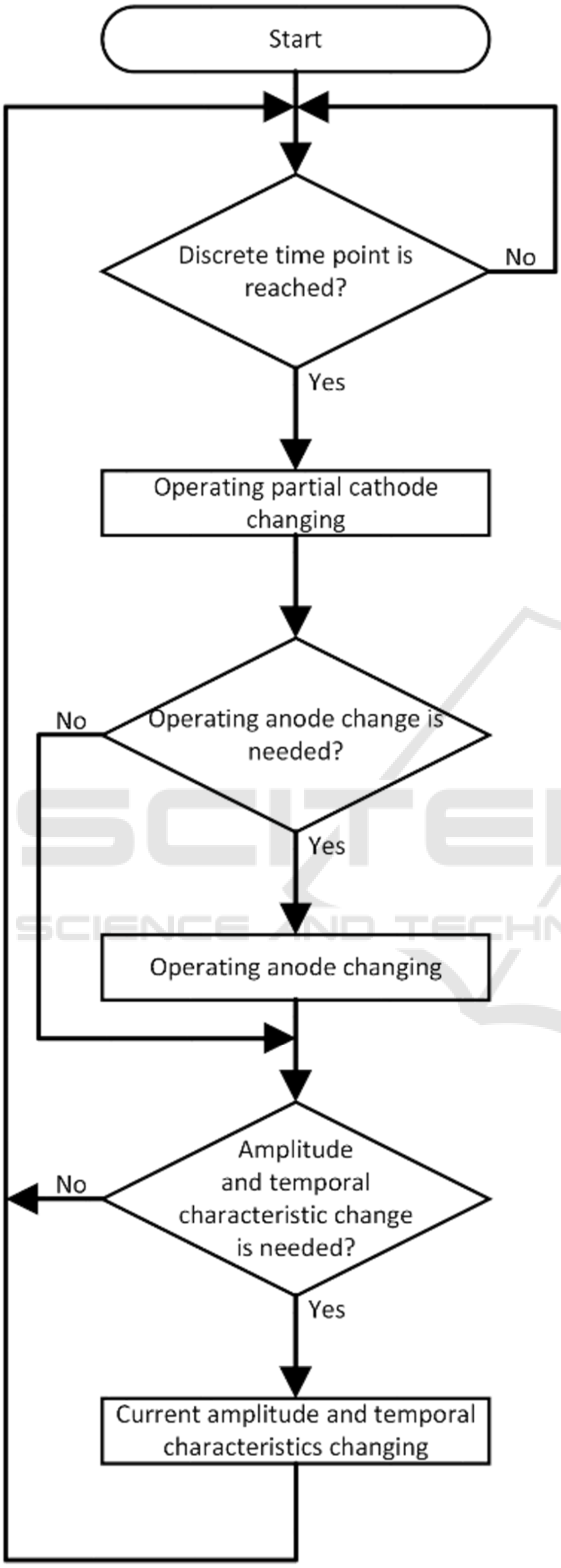

Figure 4: Neuro-electrostimulation microcontroller algorithm.

The frequency

$$\nu = 1/T \tag{3}$$

is called a frequency of the impulses “packets”.

At the discrete time point microcontroller performs several steps:

- Turns off the previous connected cathode and turns on following cathode according to the neuro-electrostimulation program. If the previous connected cathode is the latest cathode in accordance to the neuro-electrostimulation procedure than turning on of the following cathode does not occurs.
- After change of the partial cathode, if change of the anodes is required in accordance with the neuro-electrostimulation program or by doctor command, received from the control unit, microcontroller disconnects the current connected anode and connects new anode.
- If the current amplitude and temporal characteristics of field of current impulses (such as impulses “packets” repeat interval, partial impulse duration, impulse amplitude) is different from the target characteristics, set by neuro-electrostimulation program or set by the control unit, the current field characteristics are changed in accordance with the following equations:

$$A_{i+1} = \begin{cases} A_{target}, \left|A_i - A_{target}\right| < \Delta_A \\ A_i + \Delta_A, A_i + \Delta_A < A_{target} \\ A_i - \Delta_A, A_i - \Delta_A > A_{target} \end{cases} \tag{4}$$

$$T_{i+1} = \begin{cases} T_{target}, \left|T_i - T_{target}\right| < \Delta_T \\ T_i + \Delta_T, T_i + \Delta_T < T_{target} \\ T_i - \Delta_T, T_i - \Delta_T > T_{target} \end{cases} \tag{5}$$

$$\tau_{i+1} = \begin{cases} \tau_{target}, \left|\tau_i - \tau_{target}\right| < \Delta_\tau \\ \tau_i + \Delta_\tau, \tau_i + \Delta_\tau < \tau_{target} \\ \tau_i - \Delta_\tau, \tau_i - \Delta_\tau > \tau_{target} \end{cases}, \tag{6}$$

where A_i – the partial current impulses amplitude at *i* discrete time point, A_{target} – the target partial current impulses amplitude, Δ_A – the maximum current impulses amplitude increment, T_i – the impulses “packets” repeat interval at *i* discrete time point, T_{target} – the impulses “packets” repeat interval, Δ_T – the maximum impulses “packets” repeat interval increment, τ_i – partial impulse duration at *i* discrete time point, τ_{target} – target partial impulse duration, Δ_τ – the maximum partial impulse duration increment.

Rapid amplitude and temporal characteristic changes during neuro-stimulation procedure cause pain. Therefore, microcontroller limit amplitude and temporal characteristics of field of current impulses growth rate using amplitude and temporal characteristics increments.

Subsequent switch of the partial cathodes at the neck area forms spatially centered current structure. Maximum of the current density in this structure is located in the center of the anode. Ability to switch operating anode allows one to move the maximum current density point of the spatially centered current structure. This leads to neuro-electrostimulation improvements due to increase of the local neuro-electrostimulation targets number in the neck area. Improvements of the neuro-electrostimulation efficiency is achieved through involvement in the regulatory process brain structures responsible for motor, visual, auditory, vestibular functions, in addition to the ANS.

The neuro-electrostimulation subsystem is based on Analog Devices ADG5408 8-channel multiplexor chips. These chips perform partial cathodes and anodes commutation to the VCCS. At the current version of the neuro-electrostimulation devices four ADG-5408 chips are used, that allows to connect up to 16 partial cathodes and 16 anodes for the neuro-electrostimulation procedure. VCCS is formed by a current mirror with two BC807 and one BC817 bipolar transistors.

Microcontroller with built-in 12-bit digital-to-analog converter (DAC) generates control voltage. Current mirror resistor values are calculated in a way that the current source can generate a current in the range 0 to 15 mA with a load from 0 to 2 kOhms.

The ECG registration subsystem obtain signals from the first limb lead. The signal electrode 1 and the signal electrode 2 are located on the patient's hands. The RLD electrode may be on placed either on the right leg of the patient or on the any hands of the patient, if the case of the short circuiting is avoided. Standard disposable adhesive electrodes for ECG are used.

The ECG registration subsystem is based on the usage of the analog interface for ECG applications ADS1292 chip. The ADS1292 consists of a differential amplifier with the programmable amplification factor, 24-bit delta-sigma analog-to-digital converter (ADC), the device for the down sampling and digital low-pass filtration, the SPI interface, the Right Leg Drive (RLD) amplifier.

The first step of the ECG registration is filtration of the impulse interferences on the patient by a low-pass RC-filter with the 2 kHz cut-off frequency. The second step of the conversation is gain of the ECG signal by a differential amplifier, the amplified signal is supplied to the ADC and the RLD amplifier. The RLD amplifier compares the constant component of the ECG signal with the half supply voltage, amplifies the difference of signals and uses amplified difference as RLD signal. Thus, the RLD signal applied to the patient fluctuates around the half supply voltage value, which provides chip normal operation.

Delta-sigma ADC operates at 8kSPS sampling frequency, but further digital signal is filtered with help of digital low-pass filter and decimated in accordance with chip configuration. The ECG registration subsystem signal sampling rate after decimation is 500 SPS, with 131 Hz cut-off frequency of the digital low-pass filter. This frequency range is sufficient to assess the characteristics of the ANS. The filtered digital signal is sent to the microcontroller using the modified SPI protocol. In addition to the standard SPI protocol lines such as MOSI, MISO, SCLK, additional lines Data Ready (DRDY) and Conversation Start are used. DRDY signal is used by the ADS1292 to notify the microcontroller about the conversion end of the current data sample. Conversation Start signal is used for forced start of the ADC.

Usage of the ADS1292 significantly reduces devices size and improves patients comfort during neuro-electrsotimulation compared with the case, when the ECG registration subsystem is implemented using multiple chips.

3 TREATMENT OF PATIENTS WITH AMNESIC SYNDROM

Models of cognitive disorders are not sufficiently formed at the moment. So, researchers and clinicians encounter with various difficulties in development of effective approaches for neuro-rehabilitation.

The experimental studies on the laboratory animals confirmed the efficiency of the developed technology application for the restoration of the blood flow after artificial ischemia of the muscle tissue and for the normalization of the behaviour patterns after adjustment disorder (Kublanov et al., 2010). Clinical trials of the patients with epilepsy after application of the neuromodulation showed non-specific changes of the neurometabolism based on the data of the single-photon emission computed tomography (SPECT) in the cerebral cortex. The global decrease of the activity of the epileptic areas was shown by the electroencephalography features (Kublanov, 1999).

The goal of the present study is to define possibilities of the dynamic correction of the neck nerve structures conduction activity for the recovery of the cognitive function for the patients with the organic amnesic syndrome. The study was approved by USMU ethics committee (protocol #8 from 16.10.2015)

Design of serious clinical studies will be produced based on the results of this project.

3.1 Objectives and Methods

For this pilot study five male patients with clinical manifestation of the organic amnesic syndrome, as a result of brain damage caused by different pathological factors (traumatic brain injury, chronic alcohol intoxication, poisoning by household toxins) were investigated at the department of psychiatry of the Ural state medical university. All patients prior to the investigation held specialized treatment in psychological and/or neurological hospital without significant improvement. The duration of the disease varied from 12 to 24 months. Patients age varied from 33 to 48 years.

Neuromodulation with the “SYMPATHOCOR-01” device was used as the treatment course. The dynamic correction of the neck nerve structures conduction activity technique allowed affection on the processes of the autonomic regulation (through the autonomic ganglia) and stimulation of the brain stem neuronal centres (through the nerve pathways of the neck). The treatment course consisted of the 15 procedures on the span of the 3 weeks. There was no additional pharmacological treatment, except for designated previously.

Clinical data and psychometric test were used for the initial and the following evaluation of the patient’s cognitive skills: Frontal Assessment Batter (FAB) (Dubois et al., 2000), Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Instrumental diagnostics was performed with “Encephalan-EEGR-19/26 Medicom Ltd” complex and included quantitate analysis of the electroencephalograms (EEG), spectral analysis of the heart rate variability (HRV) based on electrocardiogram. The analysed features of the biomedical signals: power of the main EEG rhythms, total power of the HRV spectrum (TP), low-frequency component of the HRV spectrum (6,5-25 s) (LF), high-frequency component of the HRV spectrum (2,5-6,5 s) (HF). Clinical and instrumental evaluation was carried out by independent experts.

3.2 Results

The initial state of the patient reflected symptoms of the severe CNS damage: rough disturbance of orientation by the amnesic type, rough disturbance of the fixation amnesia, rapid exhaustion of attention, lack of cognitive efficiency, phenomena of emotional incontinence, complacency. Pronounced decrease of cognitive status and cognitive skills was defined according to the data of psychometric test. Pronounced diffusion disorganization of the main rhythms with signs of the epileptization were defined by the EEG signals analysis. HRV signals analysis revealed pronounced signs of autonomic dysregulation.

The sessions of the dynamic correction of the neck nerve structures conduction activity resulted in rather quick positive dynamic. After clinical studies patients become more active. The fatiguability and attention disorders reduced, attention and acumen significantly increase, the cognitive processes and memory improved.

The recovery of spatial and constructive activity, dynamic praxis and reciprocal coordination were noted according to the psychometric tests. The results proves recovery of the intracerebral connections. The Table 1 present summary data of the psychometric tests.

Table 1: Data of the psychometric tests prior and after treatment.

Psychometric test	Mean values of the scoring	
	prior treatment	after treatment
FAB	5,7 ± 3,1	12,0 ± 4,0*
MoCA	11,3 ± 3,0	16,3 ± 4,0*
MMSE	15,3 ± 6,2	21,3 ± 8,3*

* - significance of the difference of data after treatment from data prior treatment, $P<0,05$.

The comparative analysis of the EEG quantitative features prior and after neuro-electrostimulation showed recovery with the increase of the alpha-rhythm power, suppression of the diffusion delta-activity and paroxysmal patterns “acute-slow wave”. Results of EEG signals analysis concludes significant normalization of functional processes in the CNS.

The comparative analysis of the HRV signals prior and after neuro-electrostimulation noted the increase of the total power of the HRV and change of the autonomic balance, defined by the LF/HF ratio. The autonomic balance became normal. That concludes normalization of the autonomic regulation processes which in turn provide conditions for the recovery of the lost functions. The Table 2 presents data of the HRV spectrum features changes.

Table 2: Data of the HRV spectrum features prior and after treatment.

HRV spectrum features	Mean values of the spectrum features	
	prior treatment	after treatment
LF/HF	6,39 ± 2,4	2,2 ± 0,7*

* - significance of the difference of data after treatment from data prior treatment, P<0,05.

4 CONCLUSIONS

The results of the study demonstrated high potential of the dynamic correction of the neck nerve structures conduction activity technique to recovery of the cognitive functions. Apparently, the technique is capable to activate neuroplasticity processes and recover of the autonomic regulation in the whole organism.

Analysis of the recorded data allows one to formulate hypothesis about the formation mechanisms of the clinical effects for the developed neuromodulation method. The main ideas of the hypothesis:

- cerebral blood flow is modulated due to the regulation of the arteries tone of the small and medium calibre;
- suppression of the sympathetic department of the ANS;
- stimulation of the neurotransmitters production in the brain stem nucleus;
- suppression of the pathological hypergenerator areas in the cortex;

The mentioned mechanisms provide condition for the recovery of the intracerebral connections, which certainly increase overall adaptive possibilities of the organism.

It requires full clinical trial according to the GCP rules to confirm these hypotheses.

P. K. Anochin formulated theory of the afferent syntheses. According to this theory, the proposed neuromodulation technique might be the factor which starts afferentation. The afferentation helps to limits of the systems activity freedom in order to stabilize its functions (Anokhin, 1974). However, this hypothesis needs additional verification.

The obtained results confirm efficiency of the hardware non-invasive multichannel neuromodulation for the recovery of the cognitive impairment as the result of the organic damage of the CNS. The proximate perspectives of the developed technique are the treatment of the neurodegenerative diseases and affective disorders. The following development of the non-invasive multichannel neuromodulation technique of the nervous formations for the recovery of the cognitive functions will be defined by the reliability of the knowledge about plasticity mechanisms. Biophysicist, radiophysicist, physiologists, doctors, engineers – all must take part in the reliable knowledge formation.

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