BRAIN-COMPUTER INTERFACES, COGNITIVE NAVIGATION WORKSHOP AND NEUROENGINEERING

Region- and Age-Dependent Heterogeneity of Receptors Involved in Calcium Signaling and SLC-Family Transporters in Rat Astrocytes

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Astrocytes are electrically non-excitable cells that can integrate synaptic transmission by dynamic increases in cytosolic calcium. The mechanistic details of astroglial calcium signaling and gliotransmitters release mechanisms are hotly debated now. Physiological implications of diverse spatial, temporal and biochemical activators and modulators of astroglial calcium signals and their age-related alterations are yet to be fully understood. The functional abilities of astrocytes are critically depend on the level of expression and the subtypes of receptors on their membrane. The expression values of different receptors and their exact contribution to calcium signaling are still to be fully understood.

In the present study we demonstrate region- and age-dependent heterogeneity in the expression values of genes involved in the calcium signaling pathway, astrocyte specific markers and gliotransmitters transporters. We performed differential gene expression (DGE) analysis (by DESeq2) of RNA-Seq data obtained from cortex and brainstem of P3 and P11-12 rats. Cortical astrocytes of P3 rats compared to P11-12 show statistically significant elevation in the expression of the receptors of Gs-dependent signaling pathway (such as adrenoreceptors Adrb1, Adrb2, Adrb4, adenosine receptors Adora2a, Adora2b), particularly cAMP-dependent protein kinase A (PKA), as well as increased expression of cAMP-dependent protein kinase A (PLCε) and PLCγ, the latter might be a target for different growth factors, and sphingosine kinase, which is involved in the corresponding SPHK/S1P signaling pathway. Brainstem astrocytes of P3 rats compared to P11-12 show statistically significant increase in the expression values of the receptors of Gs-dependent signaling pathway, particularly cAMP-dependent PKA and adenylate cyclase (ADCY); elevated expression of the receptors of Gq-dependent signaling pathway (such as adenosine receptor Adora1b, adrenoreceptors Adra1d and Adra1a, metabotropic glutamate receptors Grm1, Grm5), as well as expression values of CaV2 and CaV3 and PLCε. Cortical astrocytes of P3 rats show increased expression of CaV2, CaV3, components of Gs-dependent signaling pathway and ryanodine receptor RYR compared to brainstem astrocytes of P3 rats. Cortical astrocytes of P11-12 rats compared to brainstem astrocytes of P11-12 rats show increased expression of both Gs- and Gq-dependent signaling pathways as well as receptor-operated channels (ROC), such as purinergic receptors P2RX and ionotropic glutamate receptors Grin1 and Grin2.

Differential gene expression analysis demonstrated regional heterogeneity of astrocyte specific markers: GFAP (1.18 fold more in brainstem compared to cortex), S100β and AldoC (1.27 and 0.72; 1.04 and 0.84 fold more in brainstem compared to cortex and hippocampus), GS (0.45 fold lower in brainstem compared to cortex and hippocampus). RNA-Seq data were supported by immunocytochemistry. Moreover DGE analysis demonstrated different expression values of several transporters in three brain regions: SLC44A1 and SLC2A1 (1.27 and 1.30; 0.71 and 1.22 fold more in brainstem compared to cortex and hippocampus); SLC1A2 and SLC17A7 (0.94 and 1.08; 5.57 and 5.57 fold lower in brainstem compared to cortex and hippocampus); SLC16A1 (0.80 and 0.95 fold lower in hippocampus compared to brainstem and cortex).

Hippocampal astrocytes demonstrated increased ionomycin-induced lactate release in compare to cortical (by 45%) and tendency to higher Asp and Ach release. Brainstem astrocytes exerted tendency to increased choline and Ach release in compare to both – cortical and hippocampal astrocytes.

Altogether obtained data indicate on functional region- and age-dependent heterogeneity in astrocytes regarding to the expression of the receptors involved in calcium signaling, of the specific markers, as well as cell transporters and calcium-dependent and SLC9A1-mediated lactate release.

Methodological Aspects of Enactive Neurocinema Creation

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Enactive cinema (EC) is one of the directions of innovative filmmaking. Plot development can be changed depending on the viewers psycho-physiological metrics. The first attempt to create enactive movie was an experimental art project "Obsession" (2005) by Pia Tikka, the filmmaker from Finland. EC technology provides an opportunity to increase emotional influence efficiency of the movie and make it more "environmentally friendly", meaning that the plot can be developed in a more "moderate" way without any stressful details if extremely high emotional reactivity was registered among a greater part of viewers. Both, cardiovascular body reactions metrics, such as heart rate, blood pressure, respiration rate, electrical conductance of the skin etc. [4], and metrics of the bioelectrical activity of the brain [1,2,3,5] can be used as psycho-physiological correlates for objectify emotional reactions (ER) of respondents. However, EEG metrics, frontal asymmetries of alpha-activity in particular, are more appropriate for the fast evaluation of ER dynamics.

Aims

To realize innovative approach in development of EC it is necessary to create the algorithms of relevant psycho-physiological metrics analysis in real time that can be followed by automatic decision in favour of one or another version of the plot.

The aim of the current research was to develop the algorithms of automatic plot development choice, which would cause more relevant state, based on an assessment of the viewers' ER.

Methods

In the pilot study we used three versions of the same video that differ from each other by varying plot fragments, related to specialities of forthe interpretation main part of the video. The shortest version – version 1 has been used as a base. Versions 2 and 3 contained additional fragments, 1 min. 20 sec. and 2 min. respectively. That subsequent fragments specified and expanded the follow plot development.

The plot development choice was made depending on the EEG metrics that were registered during the 2 min. introduction with parameter of alpha-activity asymmetry in frontal areas as an marker of respondent's positive and negative emotions [2,3]. The shortest version of the plot was shown to the respondents when negative emotional state was registered during the introduction, the longest version (v.3) was demonstrated when asymmetry metrics was quite high (confirming positive emotional reaction to the video). Version 2 was shown to the audience with average metrics.

Psycho-physiological metrics registered simultaneously for 5 respondents who were sitting in chairs in the cinema while looking at the same screen. EEG was analysed in real time. Thus, intensity and direction of ER changes for the group in general has been taken into account for the plot choice decisions.

50 respondents participated in the study (27 men and 23 women between the ages of 18 to 50), all right-dominated based on the leading eye and hand.

Results

This study allowed us to reveal relevant psycho-physiological metrics that can be used for evaluation of viewers ER in real time. We also got the control meanings for such metrics which can be used for ER ranking. The group analysis and decision-making algorithms were built that provide an opportunity to choose plot development direction in real time depending on the audience.

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Steady State Visual Evoked Potential Based BCI Study in Overt and Covert Attention

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Introduction

Brain-computer interfaces (BCIs) have potential to help severely disabled people by translation of the intentions of subjects into a number of different commands. Due to its safety and high time resolution, electroencephalogram (EEG) based BCIs have become popular and various designs using different signals (e.g. P300, oscillations) have been proposed. Among them, steady state visual evoked potentials (SSVEPs) are particularly attractive due to their high signal to noise ratio (SNR). In this study, we proposed a four-class BCI design based on SSVEPs to study the differences between the overt and covert attention.

Methods

Four circles with individual flickering frequencies (5.45, 8.57, 12 and 15 Hz) were presented to healthy participants on an LCD monitor. EEG was recorded from 60 channels with three electrooculogram (EOG) channels in 30 trials. In each trial, subjects focused either on the fixation cross or one of the four circles and paid attention to the circle indicated by a red oval frame for three seconds. Decision tree, Naïve Bayes and K-Nearest Neighbor classifiers were used to evaluate the classification performance using features generated by canonical correlation analysis.

Results

The offline classification accuracy for the overt attention was positively correlated with the duration of stimuli and was more than 90% when it was longer than two seconds. The accuracy dropped drastically in the covert attention case. Discussion: Classification performance for the overt attention condition validates the robustness of the SSVEP-based BCIs. However, different classification approaches should be developed in order to classify the covert attention responses.

Experimental Measurements of Human Brain Noise Intensity in Perception of Ambiguous Images

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The human brain is likely to be the most convoluted and enigmatic object for the comprehensive studies. Due to their outstanding importance and the extraordinary complexity, the investigations of the brain require the active interdisciplinary cooperation of the scientists belonging to the different branches of science. In the present work we study cognitive brain activity in visual perception of ambiguous images being just one, but a very exciting task among an enormous number of open problems of brain researches. We propose the theoretical approach associated with the experimental technique to quantitatively characterize cognitive brain activity in perception of ambiguous images. The internal noise seems to plays an important role in the visual perception of such images. Based on the developed theoretical background and the obtained experimental data, we introduce the concept of effective noise intensity characterizing cognitive brain activity and propose the experimental technique for its measurement. The developed theory, using the methods of statistical physics, provides the solid experimentally approved basis for further understanding of brain functionality. Our theoretical and experimental findings are in excellent agreement with each other. The rather simple way to quantitatively characterize brain activity connected with the perception of ambiguous images may be a powerful tool to be used, e.g., in neurotechnology, as a braincomputer interface task, and in medicine for diagnostic and prognostic purposes. We expect that our work will be interesting and useful for scientists carrying out interdisciplinary research at the cutting edge of physics, neurophysiology and medicine.

Modern Trends in Brain-Machine Interfaces

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Considerable advances in brain-machine interface (BMI) technologies bring medicine closer to solving such challenges as treatment of paralysis and sensory disabilities caused by neural trauma and diseases. Toward this goal, there is an ongoing research on prosthetic limbs controlled by brain signals, and neural stimulation systems that restore sensations by stimulating sensory brain areas. Not so long ago depictions of such BMIs could be found only in science fiction. Nowadays, even the most futuristic ideas are becoming real. Several recent studies have demonstrated direct functional connections between the brain and robotic arms. Significant achievements have been made in the systems that restore hearing, vision, vestibular function and tactile sensations to people who suffer from sensory loss.

In addition to medical applications, BMIs are being developed for augmentation of brain function in normal humans. Examples include BMIs for computer gaming, and neurofeedback systems that detect drowsiness in long-distance drivers. In the future, BMI-based technologies will lead to new means of communication and hybrid systems that merge the nervous systems with artificial neural nets.

BMIs are an interdisciplinary field that involves neurophysiologists, neurosurgeons, neurologists, robotic and electrical engineers, mathematicians and programmers. Facilitated by these collaborative efforts, BMI filed is developing very rapidly, with the number of publications growing exponentially.

Current BMIs can be classified into:

1. Motor BMIs. These systems record neural signals in the brain motor areas and transform them into control commands to external devices. Aided with motor BMIs, paralyzed patients can control prostheses of the arms and legs, and motorized wheelchairs.
2. Sensory BMIs. These are systems for restoration of vision, hearing, tactile sensations, proprioception and vestibular functions. In a typical design, sensory information is collected by an artificial sensor and transmitted to the brain using electrical stimulation of the brain sensory areas.
3. Cognitive BMIs. These devices decode higher-order brain signals, such as neural representation of decision making, emotions, and even thoughts.

A large number of methods have been developed for sampling neural signals and utilizing them in BMIs. These methods can be subdivided into two major classes: invasive and noninvasive recordings.

Noninvasive BMIs are safe to use and easy to implement. These include systems based on electroencephalography (EEG), magnetoencephalography (MEG), near-infrared spectrometry (NIRS), and functional magnetic resonance imaging (fMRI). Notwithstanding a number of advantages of these methods, their generally have low information transfer rate and are susceptible to artifacts. Additionally, noninvasive BMIs often require a considerable degree of concentration from the user, leading to fatigue.

Invasive BMIs utilize brain implants placed by a neurosurgeon on the brain surface or inserted into the brain tissue. With these methods, activity of single neurons and their populations can be recorded, which enables high-quality decoding. Modern invasive BMIs incorporate multiple recording channels. Invasive BMIs are also used to stimulate nervous tissue. Several clinical trials of invasive BMIs in humans have been already conducted.

The future steps in this field include:

- Development of clinically relevant, bidirectional, multichannel BMIs that both decode neural activity and deliver sensory information to the brain.
- Development of advanced robotic prostheses capable of restoring mobility of paralyzed limb. These include exoskeletons, prosthetic limbs and functional electrical stimulators that activate subjects' own muscles.
- Research on mathematical algorithms for decoding of brain activity. It is expected that this work will generate both efficient decoders for BMIs and new theories of brain processing.
- Development of multidisciplinary collaborations.

Overall, BMIs are definitely the technology of the future.

Device for Electrophysiological Signal Recognition and Data Transmission on Wheelchairs

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Aims

In this work we present the results of the first tests of a device capable for detecting EMG signals recognition and data transmission on wheelchairs.

Methods

In obtained results we have used electrophysiological signal, such as obtained from electromyogram (EMG), increases the effectiveness of systems for external device control: wheelchairs.

Results

It's obvious that development of a high-accuracy device that allows for continuous recording of physiological signals and transmits data to the external device (wheelchair) can yield very inspiring results. We have carried out a truly multidisciplinary study, at the first stage of which a prototype model of such device was created and tested. It was demonstrated that the signals obtained with our device were identical to those obtained with reliable analytical tools.

Conclusions

The results of EMG experiment showed the considerable advantage over joystick control. Due to the increased classification accuracy and flexibility, a device for EMG wheelchair control is more reliable and exhibits the new opportunities and freedom level for people with disabilities. The obtained results lead us to conclude that EMG recording can be used as alternative method for wheelchair control. We assume that improvements to the system and simultaneous use of various physiological signals will significantly help people with disabilities in a wheelchairs control.

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A Human-Computer Interface Based on Electromyography and Factors Limiting its Performance

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Surface electromyographic (sEMG) signals represent a superposition of motor unit action potentials that can be recorded by electrodes placed on the skin. We propose a human-computer interface based on sEMG that provides a combined command-proportional control by hand gestures (see [1] for details) with two degrees of freedom for a flexible movement of a cursor on a computer screen and allows simulating "mouse" clicks. We use an artificial neural network (ANN) for processing sEMG signals and gesture recognition both for mouse clicks and gradual cursor movements. Figure1 shows the general scheme of signal processing.

Analyzing different user groups we have found statistically significant differences between male and female subjects and between physically trained and not trained people. To get a deeper insight we have introduced the synergist-antagonist coefficient (CSA) that estimates the degree of "muscle cooperation". Experimental data suggest that the success of sEMG interface depends strongly on CSA. Thus, a significant difference between physically trained (practicing sports or other activities connected with manual small motility) and not trained people can be explained by the fact that training hand muscles and related brain circuits in everyday life may lead to a more efficient motor control. The higher interface performance found for male subjects can be connected with variations in the body composition and, especially, in the content of fat tissue. Indeed, we have revealed statistically significant correlation between the classification error and the body fat.

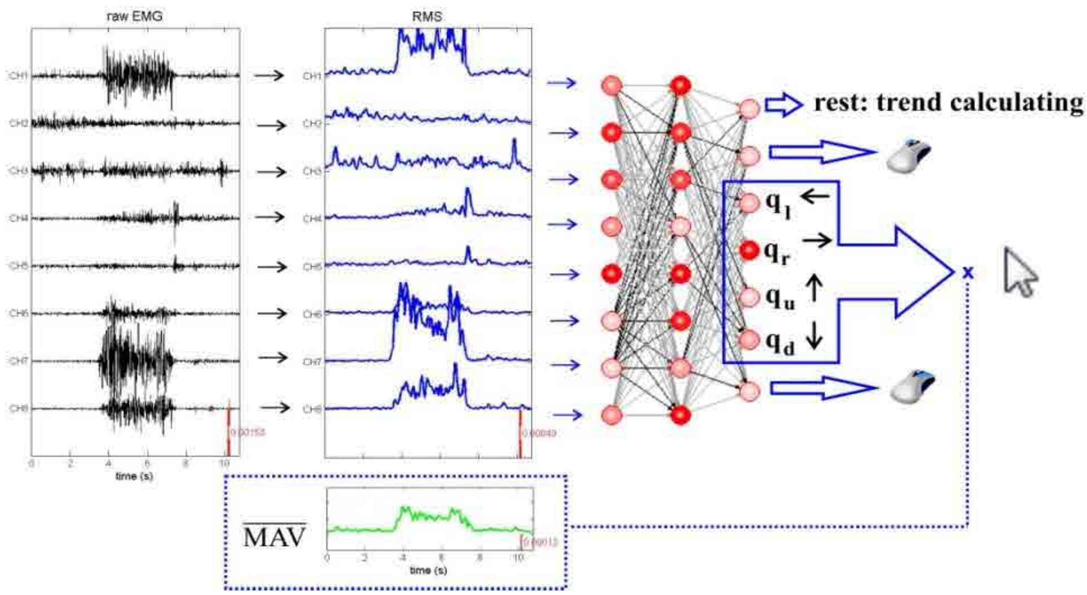

Fig.1. *Information flux in the MyoCursor system. Raw sEMG activity is mapped into cursor movements and mouse clicks in Windows OS. First RMS and MAV activity is evaluated. RMS pattern is fed into the input layer of an artificial neural network with one hidden layer. The network output from seven neurons provides two commands for mouse-like clicking and four commands for cursor movements. These are multiplied by the MAV to gain the cursor speed*

Thus, both the muscle efficiency and body fat influence significantly the performance of the sEMG-interfaces. Our data suggest that their influence is independent since we found no significant correlation between synergist-antagonist coefficient and body fat. Figure 2 shows a regression plane that allows establishing a power-law and exponential relation of the classification error with CSA and body fat, respectively.

The results also suggest that personal performance can be improved by training the user. Two subjects have shown positive dynamics in the performance and synergist-antagonist coefficient after several days of training, which included sEMG-feedback and playing a testing game with sEMG-interface.

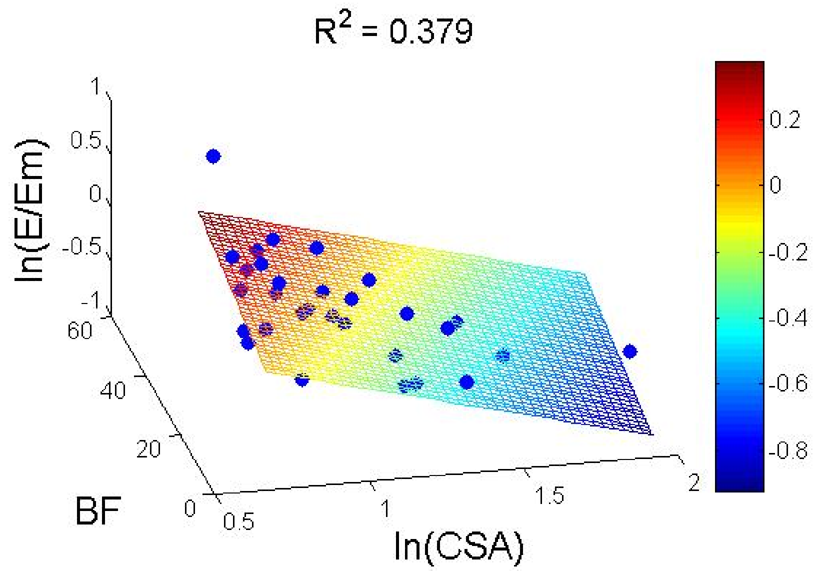

Fig.2. Dependence of classification error,ln(E/Em), (E is the error and Emis its median) on the body fat, BF, (in %) and the coefficient of synergists-antagonists, CSA, and linear regression

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Fixation-Based Eye-Brain-Computer Interfaces: Approaching a Better Human-Computer Symbiosis

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Computers are powerful tools to augment many of our intellectual abilities. However, the effectiveness of our interaction with computers depends on interfaces between them and our brains (Engelbart, 1962).

The graphical user interfaces (GUIs) and the input devices compatible with them, such as computer mice, have made the way we send commands to computers relatively fast and fluent. Can we further improve the interaction? When we fixate a GUI button or a web link with gaze and decide that we should click on them, is it really necessary to approach them, e.g., with a cursor by manually moving a mouse, and then to click the mouse button with a finger? Our gaze already indicates the position on the screen and the existing eye trackers are able to report this position. Can we design such a brain-computer interface (BCI) that could reveal our intention to click so promptly and reliably that our interaction with computers would become more effective than in the case of using conventional input devices?

Mental imagery based BCIs were already applied for supplementing the gaze based interaction with a "mental click", but the click in their operation required additional time of the order of seconds, evidently contradicting the idea of fluent control. It is much more desirable to recognize the intention to act on a certain screen position directly from brain activity patterns that accompany intention-specific fixations (Velichkovsky and Hansen, 1996).

The first attempts to implement this approach were made by Zander and colleagues (Protzak et al., 2013). They differentiated the spontaneous fixations and the fixations used to control a computer using the electroencephalogram (EEG) features. However, the fixation threshold for issuing a command in these studies was too long (1 s), so that again the interaction could hardly be considered as fluent. Moreover, the participant task was too simple compared to real-life task.

To study the issue in more complex settings, we developed a gaze controlled computer game EyeLines and recorded

EEG when 8 participants played it with their gaze only. Moves in the game were made in "control-on" mode of the game with fixations exceeding 500 ms threshold. In the "control-off" mode, fixations did not led to actions, and 500 ms or longer spontaneous fixations were collected. A special procedure was developed to make sure that the analyzed EEG intervals were not contaminated by the artifacts related to eye movement.

The EEG during controlling but not spontaneous fixations showed pronounced negativity in the posterior cortical areas starting early in the course of fixations. Using a simple feature extraction algorithm, greedy feature selection strategy and a linear classifier committee, we obtained, on average, a better than 35% true positive rate for controlling fixations while keeping the false alarm rate at about 10% on the test data with 5-fold cross-validation, much above the random level. More elaborated feature extraction algorithms are currently being tested.

Moreover, a two-threshold strategy was developed to enable smooth interaction even with the current relatively low true positive rate. When a fixation exceeds the first, short (e.g., 500 ms) threshold, the BCI is applied to detect the intention to act on the fixated location. If the BCI misses the intention, the user still may issue the command by continuing fixating the same position until the second (e.g., 1000 ms) threshold is exceeded. Since spontaneous fixations of this length are rare, it is safe to execute a command at this time even without confirmation from the BCI; alternatively, a confirmation from the BCI can be required again but with a low BCI threshold. With such a strategy, the users may develop a more stable EEG pattern associated with controlling fixations, because this will lead to faster move execution.

Our results imply that the "eye-brain-computer" interfaces (EBCIs) can not only helping neurorehabilitation, as the typical BCIs (Kaplan, 2016), but also can be used by healthy persons. Fast converting of intentions into computer actions without using any supplemental tasks (such as computer mouse manipulation, as well as special mental imagery or attention to external stimulation for activating a BCI) may make certain tasks involving interaction with computers especially fluent. This will open new perspectives for unfolding the full scale of benefits from augmenting brain function with the power of computers.

At the conference, these prospects will be discussed within a more general framework of our current and planned studies, including the search for new intention markers both in the EEG and the magnetoencephalogram (MEG), investigating the factor of the feeling of agency and free will in the use of BCIs, and online interaction of the users with different types of BCIs and EBCIs.

Acknowledgements

Parts of this work related to the specific methods of intention marker detection, their use in the EBCIs and the studies of feeling of agency and free will were supported by the Russian Science Foundation, grant 14-28-00234.

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BCI Matrix Speller Based on Coded Visual Evoked Potentials

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Aims of the study

Brain-computer interface (BCI) is a system that utilizes neurophysiological correlates of attention to establish communication with computer. The most popular type of BCIs is BCI based on visual evoked potentials (VEP BCI), for example P300 BCI or steady-state VEP BCI. Here we examine another paradigm – BCI based on code-modulated visual evoked potentials (C-VEP BCI). Within this approach, m-sequence [1] is used as pattern of visual stimulation. The crucial feature of such sequence is its autocorrelation function that has only one peak, and equals zero in all positions except this peak. Circular shift is introduced, and resulting shifted sequences are used to determine flash pattern of LEDs or elements of a computer screen. When user gazes at the elements, flashing this pattern, code-modulated response is generated [2]. This response can be extracted using canonical correlation analysis, and used to identify the target that has been chosen by user. C-VEP BCI combines the best characteristics of T-VEP and F-VEP BCI: it doesn't require long training and it is possible to introduce many different commands at time, thus enhancing ITR.

The aim of this work was to examine differences in the evoked potentials and BCI performance in response to different stimulation sequences.

Methods

20 healthy adults (10 males and 10 females) with normal or corrected-to-normal vision participated in the experiment. Visual stimuli were presented on a LCD monitor with refresh rate 120 Hz. 32 targets were arranged as a matrix. Targets were labeled with Cyrillic letters. Each target was altering between black and white with pattern derived from 64-bit binary m-sequence. The period of the sequence was 1 second. Two flashing modes were present: "straight pattern" ("1" bit of m-sequence denotes white state of stimuli, "2" denotes black), and "inverse pattern", derived from the same m-sequence by inverting it (XORed with 64 zeros). EEG was recorded from 8 channels: Pz, P1, P2, PO1, PO2, PO3, PO4, POz at 500 Hz. Learning session was followed by online mode, where participant tried to select all 32 targets. Classification algorithm based on CCA was employed in online mode, classifying EEG samples of variable length, up to 5 seconds long.

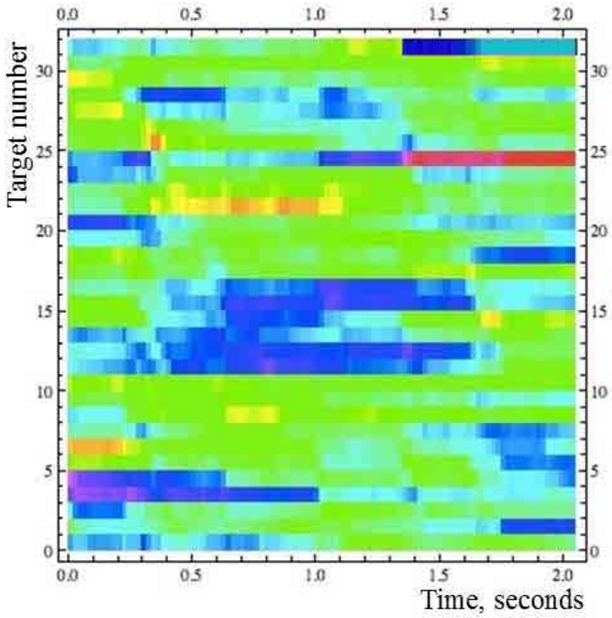

Fig.1. Correlation coefficient between single trial EEG in response to target number 25 and average EEG response from learning session, visualized over time. Red color depicts maximum correlation coefficient

Conclusions

We have successfully created BCI based on C-VEP paradigm. Its characteristics in terms of number of commands, ITR and accuracy make this type of interfaces a viable replacement for traditional and well-proven t-VEP P300 BCIs. The main weakness of C-VEP spellers is visual environment, which is too aggressive and may lead to operator tiredness. The nature of differences between evoked patterns proposes complex mechanism of EP generation.

Acknowledgements

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Rapid SSVEP Mindspelling Achieved with Spatiotemporal Beamforming

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In brain-computer interfacing (BCI) based on steady-state visual evoked potentials (SSVEPs), the number of selectable targets is rather limited when each target has its own stimulation frequency. One way to remedy this is by combining frequency- and phase-coding. We introduce a new multivariate spatiotemporal filter, based on Linearly Constraint Minimum Variance (LCMV) beamforming (van Vliet et al., 2015), for discriminating between frequency-phase coded targets more accurately, even when using short signal lengths, than with (extended) Canonical Correlation Analysis (CCA) that is traditionally posited for this stimulation paradigm (Nakanishi et al., 2014). Our results show that with our new decoding scheme and spatiotemporal beamforming, accurate spelling can be achieved even in an online setting.

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The Control Human Phantom Fingers by Means of P300 Brain-Computer Interface for Neurorehabilitation

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Aims of the study

Motor imagery (MI) that triggers restructuring of the motor act plan in neuronal networks can be as effective for the restoration of impaired motor coordination as the actual implementation of the movement. However, despite the seeming simplicity of MI, whether it is effective in triggering cortical restructuring depends on mental effort intensity, stability and direction. The feedback loop can be provided by brain-computer interface (BCI) technologies based on EEG recording and mu-rhythm depression that allow for detecting mental representations of movements and transforming those events into commands for controlling the external objects. Using this skill during training sessions is an effective trigger for adaptive plasticity processes in the corresponding brain structures [1]. The weakness of this approach is the extremely low level of differentiation of mental movement representations in relation to their subsequent BCI-based identification.

Only 2-3 motor images can be reliably identified by BCI on the basis of motor imagery. It is not enough in case there is a necessity to establish several feedback channels for mental rehearsal of fine motor skills, such as movements of individual fingers, which are the hardest to restore. At the same time, there is a BCI technology that uses EEG for the reliable detection of human focus of attention on external screen characters and allows for further creation of a library that contains no less than 36 commands [2]. Detection of the attention focus is based on EEG responses to short flashes of external objects, such as symbols on the screen; response to a target stimulus is identified on the basis of specific response parameters, a P300 wave in particular. Still, BCI-P300 seems to have some prospects for being used in rehabilitation as a communicator only, such as for spelling.

In this work we test the hypothesis that BCI-P300 can be used in a non-standard manner: as a basis for a training simulator for improving fine motor skills (of fingers) with a multichannel feedback. For this simulator, the anthropomorphic hand phantom with movable fingers can be used as an actuator. We speculate that using a BCI-P300 system proposed in this work, an individual will be able to control phantom finger flexion by focusing his attention on the fingers. The onset of finger movement will indicate the sufficient intensity of mental effort aimed at focusing attention on the process.

Methods

The study enrolled 12 volunteers (18-25 years of age). Above the right arm of the subject covered with non-transparent fabric, the anthropomorphic hand was placed, with movable fingers connected to servo-motors by means of flexible cords. Light markers (LEDs) were attached to the distal phalanx of each phantom finger. Turning them on and off was a visual stimulus for event-related potentials (ERPs) recorded by EEG (NVX52,MKS, Russia). To identify ERPs associated with target stimuli, i.e., flashes of the light markers on the phantom finger that the subject's attention was focused on, Fisher linear classifier based on Fisher linear discriminant analysis (LDA) was used; its output was transformed into a finger-flexion command for the phantom if the preset threshold was exceeded. During the experimental session, a randomized sequence of flashes for each phantom finger was presented to the subject necessary to perform one command, i.e., to flex one phantom finger that the subject's attention was drawn to by flashes. Each command was preceded by instructing the subject on what phantom finger had to be chosen. Every subject had 20 experimental trials spaced by small breaks; the results of the trials were used to assess how effectively the subject operated the hand phantom. Immediately before the experimental session, the classifier was trained using non-random sampling of target and non-target ERPs. The effectiveness of phantom finger control was assessed based on control accuracy parameters, namely, the number of right, wrong or absent phantom finger flexions while focusing the attention on a certain phantom finger.

Results

It was shown subjects rarely fail to select the target finger for flexion. In average, there are no more than 1.5 errors in 20 trials. But in a greater number of cases (5-6 depending on the operating mode), subjects fail to initiate flexion of any finger leaving the phantom hand motionless. Wilcoxon test showed significant differences ($p<0.05$) when comparing the number of type 1 and type 2 errors for each experimental mode. Setting a non-target finger in motion is an error possibly related to the unstable attention focus, as a result of which attention is drawn to the non-target finger, and the latter is wrongly detected as a flexion target.

Conclusions

The BCI-P300 technology can enable generation of commands for mental control of fingers of the human hand phantom with reliability of no less than 69%, which is sufficient to develop a fine motor skills neurosimulator. The majority of the BCI-P300 operator's errors in controlling the fingers of the human hand phantom are associated with insufficient focus on the signals of the light markers placed on phantom fingers, which necessitates the improvement of the stimulus media.

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Multidimensional Dynamic Chaos in Cerebellum

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The cerebellum of vertebrates is a part of the brain, where all fine details of physical and mental actions are elaborated and stored. Its cortex unique regular and homogeneous structure presents great temptation for those, who are interested in physical modeling of brain parts, especially due to the fact that at least 70% of human neurons are the granular cells of the cerebellum. We elucidate and explore here the features of the cerebellar operations, which are not yet widely exposed.

It was enigmatic until recently why the complex spikes activity of the cerebellar Purkinje cells almost permanently looks chaotic. It happens even at those times when the simple spikes activity of the Purkinje cells is heavily correlated with, say, movements of the limbs. The enigma is due to the fact that both the liana cell (the cell in inferior olives that sends a climbing fiber ("a liana") to the Purkinje cell), which controls a given Purkinje cell, and the Purkinje cell itself (via the parallel fibers) get strong afferent signals from limbs in these conditions. What prevents movement-related modulation of the liana cell activity?

The answer, first given by Michael Mauk and his collaborates [1, 2] lies in bidirectional plasticity of granule cell to Purkinje cell synapses, which is controlled by activities of granule cells, the activity of Purkinje cell and activity of its liana cell. The direction of the plasticity depends on combination of the above mentioned activities. As the result of the plasticity processes the synapses from granule cells to Purkinje cell are modified in such a way that the sum of the input signals to liana cell in standard routine tasks becomes practically constant in time domain. This property yields the absence of phase modulation of Purkinje cell complex spikes. The possibility of such equalization of the liana cell membrane potential is provided by the feedback from the Purkinje cell to the liana cell. Signals from liana cell to Purkinje cell are delivered as discrete impulses with the mean frequency of one impulse per second. The feedback arrives to liana cell as essentially continuous signal, as Purkinje cell firing frequency is in the range 20-200 imp/s and there are (on average) 10 Purkinje cells, involved in the loop with one liana cell. The consequence of the described functional arrangement is that the Purkinje cell firing frequency accurately follows bumps and pits of the sum of the non-cerebellar inputs to the liana cell. In fact the Purkinje cell output precedes the input to liana cell for the amount of the time delay of signal propagation from Purkinje cell to liana cell.

This is the general idea, which has been initially formulated in 1997 by Mauk et al. (published in 1998 [1, 2]), and has been supported by mathematical proof of the (exponential) stability of the signals in the loop (Purkinje cell) → (deep cerebellar nuclear cell) → (liana cell) → (Purkinje cell) [3]. Moreover, there were signs that instead of maintaining plainly constant (with random noise) membrane potential of the liana cell the described cerebellar loop provides dynamic chaotic oscillations of this potential, which is observable in records of interspike intervals of the liana cell activity and, indeed in properties of the Purkinje cell complex spikes [4-6]. The dynamic chaos in this case is generated in the system with the number of variables equal to the number of synapses of parallel fibers, which monitor the activity of the Purkinje cell and are the subject of plasticity due to interaction of the synapse plasticity with the relations of the firing time of the liana cell and presynaptic activity of granule cells.The data of computational experiments on properties of activity of Purkinje cell and liana cell, subject to emerging chaotic oscillations will be demonstrated in the talk. The role of dynamic chaotic patterns of climbing cell membrane potential and spike firing patterns will be extensively discussed following the initial line of [6]. A particular attention will be paid to the role of cerebellum in creative tasks, which has been recently revealed in f-MRI tracked experiments with non-standard figure drawing [7].

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The Dependence on Noise of STDP-Driven Synchronization at Neural Network

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Synchronization in neuron networks is known to play an important role in brain information processing [1]. Earlier we showed the synchronization of neural network response on spatially localized periodic stimulation [2]. Because of spike-timing-dependent synaptic plasticity (STDP) the steady-state spatial pattern of the weights rearranged and these changes underlay the synchronization phenomenon. Here we investigate the role of neural noise in the synchronization.

The network consisted of synaptically coupled spiking neurons simulated by Izhikevich's model [3]. 400 excitory and 100 inhibitory neurons were used. Short term (Tsodiks-Markram model, [4]) and long term plasticity (STDP) took place. Each neuron was exposed by a mutually independent and uncorrelated Gaussian white noise $\sqrt{2D}\xi_i$ with variance D $\langle \xi_i(t) \rangle = 0$ $\langle \xi_i(t)\xi_j(t') \rangle = \delta_{ij}\delta(t-t')$,

The stimulus was introduced to the network by activation of an arbitrary chosen group containing one inhibitory and five excitatory neurons located in the same small network area. Each stimulus made all the neurons from the chosen group to fire, which in turn could produce population burst of spikes. Frequency of stimulation was 10 Hz. If the synchronization appeared all stimuli led to bursts generation, so frequency of bursts equal to 10 Hz was a criterion of the synchronization.

We varied noise variance D and registered time required for network synchronization. For illustration purpose we introduced the synchronization index which was equal to 1/t, where t – time of stimulation to synchronization. The Fig. 1A shows examples of different evolutions of bursts frequency in the condition of various noise variance. When noise was small there were no bursts and accordingly no synchronization (Fig. 1A, 1). At increase of noise variance some unstable synchronization appeared (Fig. 1A, 2). In the conditions of middle noise the perfect synchronization took place (Fig. 1A, 3). At further increase of noise variance unstable synchronization could appear again (Fig. 1A, 4). Finally in the conditions of big noise there was the lack of synchronization (Fig. 1A, 5). The Fig. 1B summarizes the dependence of the synchronization on level of neural noise.

It should be noted that the transition from asynchronous to synchronous dynamic behavior in the system is carried out through the intermittent behavior, which is reflected in the alternation of synchronous dynamic areas with areas where there is no synchronization (Fig.1A 2, 4 "unstable synchronization") while all control parameters of the system are constant. This type of transition from synchronization to the asynchronous state is characteristic of the wide range of non-linear dynamical systems [5, 6]. The supercritical parameter in the system appears the noise variance, which is responsible for the existence of intermittent behavior and its defining characteristics.

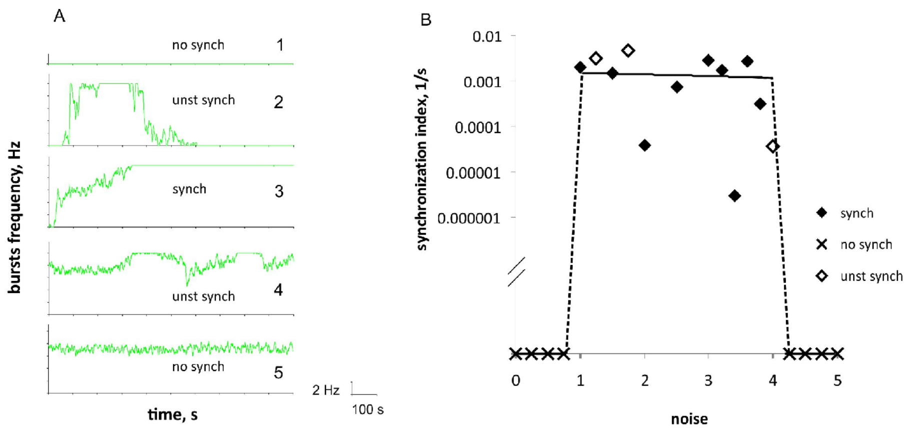

***Fig.1.** The dependence of the network synchronization on neural noise variance. A) examples of different evolutions of bursts frequency: 1) the absence of bursts and accordingly lack of synchronization in the conditions of small noise; 2) unstable synchronization at increase of noise level; 3) the synchronization in the conditions of middle noise; 4) unstable synchronization at further increase of noise variance; 5) the lack of synchronization in the conditions of big noise. B) The dependence of the synchronization index on level of neural noise*

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Synchronization of Two Coupled Electronic Neurons via Memristor

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Design of electronic neuron networks capable to reproduce brain functions in silico is one of the most intriguing challenges in modern science and engineering. Such systems would permit to develop new generation of information processing technologies based on brain computation principles. Another interesting application is to make an interface between electronic circuits and living neurons for biomedicine. The electronic circuits should resemble all dynamical regimes of nerve pulse generation in single neurons. In the network design, the crucial point is synaptic coupling between neurons providing reliable signal transmission. Moreover, the coupling strength can be variable depending on the ongoing neuron activity, what is called synaptic plasticity.

In this work, the dynamics of two electronic neuron oscillators coupled via memristor has been investigated. Each neuron is implemented as pulse signal generator based on the FitzHugh-Nagumo equations. This model provides a qualitative description of the main neurons' characteristics including the excitable and self-oscillatory dynamics. Different neuron-like signals (single pulse, transients, self-oscillations) can be observed by changing threshold parameter. Memristor is realized in a simple metal-oxide-metal nanostructure demonstrating reproducible resistive switching effect [1].

After testing and tuning of the master and slave neuron oscillators their coupling by memristor was implemented. The output signal from the master neuron was conveyed to input of memristor. Output signal from memristor sent to the input of the slave neuron. Such unidirectional signal transmission implements the functionality of excitatory synaptic coupling.

Such model mimics the interaction between synaptically coupled brain neurons, where the memristor imitates neuron axon. The resistance can be continuously varied, and such analog variation of resistance provides a useful model of key features of the biological synapse, and memristor as synapses in neuromorphic circuits can model synaptic plasticity. The synaptic connection is modelled by output signal from memristor. It is experimentally demonstrated that such connection can provide forced synchronization with locking ratios 1:1.

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3D Biodegradable Scaffolds Produced by Microstereolithography Tecnique for Neural Tissue Engineering in Experimental Traumatic Brain Injury

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Aims

Traumatic brain injury (TBI) occurs, as a result, of direct mechanical insult to the brain, and induces degeneration and death in the central nervous system (CNS). Unfortunately, TBI causes extensive loss of cerebral parenchyma; however, no strategy for reconstruction has been clinically effective. It has been shown that one of the promising approaches used in regenerative medicine are three-dimensional biocompatible scaffolds capable to induce the growth of nerve cells. Such scaffolds are compatible with nerve tissues and can support its recovery during regeneration. Growth of cells and development of tissues depend not only on the material of the scaffold, but also on its 3D structure [1]. To identify new ways of parenchyma reconstruction we used 3D biodegradable scaffolds produced by microstereolithography technique.

Methods

3D biodegradable scaffolds produced by microstereolihography technique from combination of the modified chitosan and hyaluronic acid of high molecular weight [2], the molecular weight of chitosan was 40–50 kDa, and the degree of acetylation was 0.30. Besides chitosan, we used the modified by a reaction with glycidyl methacrylate hyaluronic acid according to the article of O. Kufelt et al. [3].

Biodegradability of scaffolds determined estimated time of degradation within 1-3 months and a mechanism, such as enzymatic hydrolysis. Modified chitosan - hyaluronic acid scaffolds populated with adult stem cells from mouse (C57BL/6j) nasal olfactory lamina propria were transplanted into the lesion cavity of the injured cortex 7 days after TBI, and the mice were sacrificed 21 days after TBI. Sensorimotor function and spatial learning were measured using an array of function tests, MRI and the brain tissue was processed for immunohistology analysis. Recognition memory was evaluated using the Object Recognition Test (ORT) in mice on 25 day after brain injury. Memory was operationally defined by the discrimination ratio for the novel object (DIR), as the proportion of time the animals spent investigating the novel object minus the proportion spent investigating the familiar one during the testing period. The level of cytokines IL-2, IL-4, IL-6, IFN-γ, TNF-α, IL-17A, IL-10 was determined in the serum and dissociated cells of the cerebral cortex mice of the C57BL/6 using flow cytometry (FACSCanto II - BECTON DICKINSO, USA). To study the cytocompatibility of scaffolds with cultured cells we used histochemical live/dead cell viability assay.

Results

The data show that scaffolds populated by neuronal stem cells from mouse nasal olfactory lamina propria improve learning and sensorimotor function, reduce the lesion volume, and provide the migration of stem cells into the lesion boundary zone after TBI in mice, reduce the formation of glial scar. In addition, modified chitosan scaffolds reduces the amount of proinflammatory factors TNF-α, IL-6, IL-2 and normalize the content of anti-inflammatory cytokines IL-4, IL-10 locally in the brain, and on the system level. It is important to note that there was no activation of autoimmune processes, the level of IL-17A did not change after the reconstructive surgery.

Conclusions

Neuronal stem cells populated 3D biodegradable scaffolds produced by microstereolihography technique from combination of the modified chitosan - hyaluronic acid may be a new way to reconstruct injured brain and improve neurological function after TBI. These data show that neuronal stem cells from mouse nasal olfactory lamina propria induce neurogenesis and contribute to restoration of brain tissue via trophic actions. Our experiments on mice may suggest that human olfactory tissue is a conceivable source of nervous system replacement cells. Treatment with 3D biodegradable scaffolds normalize the content of anti-inflammatory/ proinflammatory cytokines without activation of autoimmune processes.

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Development of Tactile Feedback Loop Based on Skin Vibro-Stimulation for Brain-Computer Interface

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About 30% of stroke patients suffer from disorders of motor and somatosensory systems [1]. Methods of target rehabilitation of motor and sensory deficits are very important for recovery of these patients [2]. Conventional rehabilitation methods and approaches require a lot of specialized staff and are not enough effective, and for example, the United States spends $36.5 billion a year on it [3]. In this context the rehabilitation approaches based on BCI seem to be the most promising.

The main innovation of these approaches is that BCI allows you to decode the very intention to motion that occurs as a plan of action in the brain, even in deeply paralyzed people. This intention can be identified by the algorhytms and translated into a command for external executive devices: manipulators, exoskeletons, etc. Thus, human intent can be transformed into a real action even in case of strong damage of pathways between brain and the muscles. This will provide an opportunity for patients to control a training device directly by mental efforts that would make rehabilitation more effective and less demanding to support personnel.

However, despite the high level of modern development of BCI technology, including the latest advances of computer and electronic equipment, software and algorithmic approaches and neurophysiological knowledge, all these BCIs have several common disadvantages. These are low information transfer rate, very slow development and poor automation of the BCI skill. Moreover, it is impossible to control a BCI-operated object proportionally, for instance, smoothly move a cursor along the desired path. A few attempts to build a BCI feedback as a result of produced actions have been taken, some of them were successful, but all this was done either invasively or using animals [4].

Therefore, the aim of this work is to develop a suitable for human non-invasive BCI technology with non-visual feedback loop. This young technology may help to overcome the existing BCIs restrictions in operation speed and accuracy, but which is more important, to make this technology closer to the real organism with its natural sensorimotor pathways and ability to automate new skills.

The relevance of this work is that the proposed new BCI technology for humans will include feedback by means of multi-unit vibro-tactile skin stimulation. This will help to build a BCI technology that can reproduce natural mechanisms of human motor activity by means of muscles that are initially provided by the feedback with the brain.

In this study we developed a circuit which consisted of 5 independent vibro-stimulators placed on the skin surface of the shoulder girdle. The vibromotors were driven by a microcontroller through serial port of the computer and used as a sensor feedback loop. We developed a software that can be used to translate any BCI command to each motor independently with specific vibrating pattern. Decoded patterns of motor movement in EEG experiments were translated into tactile commands to the skin. Each motor generated high-frequency vibration (9000 rpm) during short period (1 sec) after the movement pattern was obtained. We hypothesize that such approach will enhance classification efficacy of the BCI system.

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