VOLGA NEUROSCIENCE MEETING 2021

August 24-27 Nizhny Novgorod, Russia

ABSTRACTS BOOK

VOLGA NEUROSCIENCE MEETING

«Chayka» Resort Hotel, Nizhny Novgorod,
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INTERNATIONAL CONFERENCE
VOLGA NEUROSCIENCE MEETING 2021
ABSTRACTS BOOK

(NIZHNY NOVGOROD, «CHAYKA» RESORT HOTEL
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Abstracts of the 3rd International Conference Volga Neuroscience Meeting 2021 include a wide range of areas of modern neurobiology: Molecular and cellular neuroscience, Biophotonics, Neurodynamics and artificial intelligence, Computational neuroscience, Cognitive neuroscience and workshop on the topic «Molecular mechanisms of aging». The main goal of the conference is to exchange experience between leading and young scientists in the field of neurobiology and artificial intelligence.

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MOLECULAR AND CELLULAR NEUROSCIENCE

The MOLECULAR AND CELLULAR NEUROSCIENCE section will bring together leading scientists and young researchers with a keen interest in the latest advances at the interface of molecular and cellular biology and imaging in neuroscience. The symposia will highlight recent discoveries in the development of the nervous system, synaptic function, brain imaging, molecular and cellular mechanisms of neurological diseases. This section presents excellent opportunities for discussion, and an insight into the latest molecular neuroscience trends and technologies.

EPIGENETIC REGULATION OF LONG-TERM CHANGES IN PLASTICITY

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Specificity of participation of a given molecular system in development of long-term changes in the nervous system is a tricky problem. Changes in balance practically of any molecular systems, as well as impairment of any signal cascade impairs long-term memory, changes plastic properties of the nervous system, but these changes do not add any new information about memory mechanisms. The hypothesis that modifications of DNA (methylation) can be related to long-tern storage of information appeared right away after discovery of the double helix structure of DNA. Any change in effectivity of the genetic system functioning automatically implies changes in functioning of all molecular systems in the neuron, and will be reflected in the role of a given neuron in the network. Still, the dominating point of view in neurophysiology is that the role of epigenetics in non-proliferating cells is small, epigenetic regulators influence all genes non-specifically. Detailed studies showed that sodium butyrate, an inhibitor of histondeacetylases, regulating the chromatin condensation levels, elicits significant changes in expression of less than 2% of genes, most of which appeared to be involved in memory formation and maintenance. Abundant publications describing specific effects of epigenetically regulated chromatin structure and regulators of DNA methylation on higher brain functions and parallel changes in expression levels mostly in “plasticity genes” suggest new mechanisms of memory formation, maintenance and extinction.

Extensive amount of literature and our own experimental data demonstrate considerable efficiency of different epigenetic agents (histone deacetylase inhibitors, DNA methyltransferase inhibitors) in regulation of long-term changes in neural networks and memory-associated behavior. Acting at different levels of chromatin organization, they work in concert to control specific expression profile for particular plasticity-related genes in neurons of vertebrates and invertebrates. Our recent preliminary results imply that chromatin rearrangements may also alter the exon composition of particular synaptic genes and genes, associated with learning and memory. Transcriptome analysis revealed noticeable variability in mapping reads to the first exons (5` ends) of some of these genes, leading to speculations about its role in the neurons.

Our results are consistent with previously published data, showing that HDAC inhibitors can selectively restore weakened memory in mollusks and rodents without altering the basal synaptic neurotransmission. Therefore, directed pharmacological influence on the epigenetic mechanisms (histone acetylation), underlying learning and memory, is able to compensate memory deficits in vertebrates and invertebrates. Development of genetic tools for selective epigenome editing represents a promising approach, giving an alternative level of regulation of gene expression with minimal off-target effects, what makes it well-suited for clinics.

Acknowledgements

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EFFECT OF THE TUMOR NECROSIS FACTOR GENE KNOCKOUT ON SENSITIVITY TO LIGHT REGIME DISTURBANCES IN MICE: THE ROLE OF BRAIN-DERIVED NEUROTROPHIC FACTOR AND BRAIN SEROTONIN SYSTEM

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Circadian disruptions such as a decrease in the length of daylight hours (short photoperiod) and prolonged exposure to artificial light at night (LAN) provoke the development of affective disorders in humans and depressive-like behavior in rodents. Often these processes are accompanied by the disturbances of Brain-derived neurotrophic factor (BDNF) production and brain serotonin (5-HT) system functional activity. The interaction of the nervous and immune systems plays an important role in the formation of behavior, especially pathological. Tumor necrosis factor (TNF) is a pro-inflammatory cytokine that represents an important component of the immune and central nervous systems. High TNF level in the brain is linked to major depressive disorder and cognitive dysfunctions. The aim was to evaluate the involvement of TNF in the effects of exposure to a) short photoperiod and b) artificial light at night on behavior, brain expression of BDNF-related genes and state of the brain 5-HT system.

Methods

The impact of exposure to a) short day (4 hours light/20 hours darkness during 6 weeks, control groups - 14 hours light/10 hours darkness) or b) LAN (150 lux day/5 lux night during 6 weeks, control groups - 150 lux day/0 lux night; all groups - 14 hours/10 hours day/night) was estimated on adult C57BL/6 (WT) mice and TNF knockout mice (TNF KO) generated on genetically pure C57BL/6 background. Behavior was evaluated in the open-field, novel object recognition and forced swim tests. The mRNA levels of genes encoding a) BDNF and its TrkB, p75 receptors and b) key elements of brain 5-HT system were determined using Real-Time PCR. The 5-HT and its metabolite 5-HIAA levels were measured using HPLC. The data were analyzed by two-way ANOVA followed by LSD post-hoc test.

Results

The short photoperiod provoked anxiety-like phenotype in the open-field test only in TNF KO mice ($p<0.05$) and impaired performance in the novel object recognition test only in WT mice ($p<0.05$), whereas the short day-induced rise of depression-like immobility in the forced swim test was more intensive in TNF KO than in WT mice ($p<0.05$). Augmented expressions of Bdnf gene in the prefrontal cortex of both strains ($p<0.01$) and p75 receptor gene in the midbrain of WT mice ($p<0.01$) were shown after short-day condition. Only WT mice demonstrated increased expression of 5-HT2A receptor gene in the prefrontal cortex ($p<0.01$), 5-HT7 receptor gene in the hippocampus ($p<0.05$), tryptophan hydroxylase-2 gene in the midbrain ($p<0.05$) after exposure to reduced daylight. Short photoperiod increased the 5-HT level in the hypothalamus of WT mice ($p<0.05$) and in the prefrontal cortex of knockout animals ($p<0.05$). While the 5-HT turnover (5-HIAA/5-HT) was augmented in the midbrain ($p<0.05$), hypothalamus ($p<0.05$), prefrontal cortex ($p<0.05$), hippocampus ($p<0.05$) of TNF KO mice.

The exposure to light at night provokes depression-like immobility in the forced swim test only in WT mice ($p<0.05$). Also, the mRNA level of gene encoding 5-HTT (5-HT transporter) was increased ($p<0.05$) and the mRNA level of gene encoding TrkB receptor was reduced ($p<0.05$) in the midbrain of WT mice.

Conclusion

Thus, TNF knockout mice demonstrated altered sensitivity to the influence of short photoperiod and significant resistance to the effect of light at night. These mice represent a promising model for studying the effects of circadian disruptions on behavior, brain neuroplasticity, and neurochemistry.

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SEIZURE-INDUCED PROINFLAMMATORY CYTOKINE RESPONSE IS MODULATED BY CB2 RECEPTORS IN THE HIPPOCAMPUS BUT NOT IN THE NEOCORTEX

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We compared cytokine responses in the neocortex, dorsal and ventral hippocampus, cortical leptomeninges, and dura matter induced by noncovulsive and convulsive seizures and analyzed the role that may be played by cannabinoid CB2 receptors in the neuroinflammatory response induced by generalized tonic-clonic seizures (GTCS). We analyzed mRNA expression of interleukin-1b, CCL2, interleukin-6, tumor necrosis factor (TNF), and transforming growth factor beta 1 (TGFb1) in 3 and 6 hours after induction of GTCS by pentylenetetrazole (PTZ, 70 mg/kg) or absence-like activity by low dose of PTZ (30 mg/kg). The low dose of PTZ had no effect on the gene expression 3 and 6 hours after PTZ injection. In 3 and 6 hours after GTCS induction, the expression of CCL2 and TNF increased in the neocortex. In 3 hours after PTZ, we also observed elevation of CCL2 expression both parts of the hippocampus. Cortical leptomeninges but not dura matter also responded by elevation of CCL2 level and a decrease in TGFb1 expression 3 hours after GTCS. Activation of CB2 receptors by HU308 suppressed inflammatory response only in the dorsal hippocampus but not neocortex. Suppression of CB2 receptors by AM630 potentiated expression of inflammatory cytokines also in the hippocampus but not in the neocortex. Thus, we showed that GTCS, but not absence-like activity, result in inflammatory response in the neocortex, dorsal and ventral hippocampus, and cortical leptomeninges, and this response is sensitive to modulation of CB2 receptors only in the hippocampus but not neocortex.

DEVELOPMENT OF MOLECULAR TOOLS FOR TARGETING THE FUNCTIONAL NEURAL NETWORKS

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It is well established now that memory performance is accompanied by cellular and molecular changes in functional neural networks (“engrams”). Therefore, investigation of learning and memory mechanisms requires novel approaches, eligible for specific manipulations with particular subsets of neurons. The third generation Tet-On 3G tetracycline-inducible expression system has a potential for specific spatio-temporal control of the “engram” cells. As its earliest versions, this system consists of transcriptional transactivator rtTA (rtTA3G) that binds to and activates the specific TetO promoter (in our case a bidirectional TetO, biTetO) only in the presence of antibiotic doxycycline (Dox), but exhibits highest sensitivity to Dox, and therefore produces minimal side effects.

In the current study we aimed to create a multifunctional platform on the basis of Tet-On 3G system for specific labeling and recording of the neural networks, becoming active during learning. Also, a properly labeled engram cells can go through a cell sorting procedure for subsequent analysis of their molecular profile.

We performed molecular cloning to generate an AAV plasmid with bright fluorescent marker mCherry and calcium sensor GCamp6s, expressed from the opposite sides of bidirectional biTetO promoter without compromising the output. Co-application of the available AAV construct (Addgene #120309) with rtTA3G, driven by *Fos* promoter, allowed us to restrict gene expression (mCherry, GCamp6s) to a specific subset of neurons, becoming active during learning (spatial control). Administration of Dox, at the same time, allowed us

to restrict gene expression to a particular time window (temporal control), minimizing number of cells with background *Fos* activity.

First, the plasmids were tested *in vitro* on HEK293T cell line. Single- (biTetO) or double-transfected cells (rtTA3G; biTetO) were treated with low doses of doxycycline (Dox, 2 mkg/ml), and compared with untreated groups 24h later. We observed background fluorescence for both mCherry and GCamp6s in untreated cells that implies some promoter leakage at rest. Application of Dox in double-transfected cell cultures significantly potentiated gene expression that went far beyond the background signal. In the series of experiments, we also examined, whether the bidirectional promoter biTetO exhibits comparable transcriptional activity in both directions. To eliminate the differences, associated with fluorescent characteristics of transcribed elements, in this set of experiments we replaced calcium sensor GCamp6s in the biTetO expression cassette to EGFP fluorescent protein with similar to mCherry parameters. HEK293T cell cultures were co-transfected with rtTA3G and a modified biTetO plasmid. Relative mRNA expression of *mCherry* and *EGFP* genes was analyzed in the control and Dox-treated cultures using quantitative PCR. Human *HPRT* housekeeping gene was used as a reference. Our preliminary results highlight comparable biTetO promoter activities in both directions. Substantial co-localization of the expressed fluorescent proteins was also verified with fluorescence microscopy. Obtained data can be relevant for functional studies, where the ratio of expressed genes matters.

At the next stage, we tested the functionality of generated plasmids *in vitro* on rat primary hippocampal neuron cultures. Genetic constructs (rtTA3G; biTetO) were delivered into neurons via electroporation at the day of seeding. In line with the previous data, we observed biTetO promoter leakage in neurons in resting conditions, as reflected in background fluorescent signals from GCamp6s and mCherry. In contrast to HEK cells, the activity of *Fos* promoter in the nervous system is tightly regulated. Therefore, induction of Tet-On 3G system in cultured neurons was triggered by Dox administration, followed by stimulation of neurons with KCl in order to activate *Fos* promoter. This combination of stimuli significantly elevated the expression of genetic constructs in cultured neurons. Summarizing, a new generated version of Tet-On 3G system is suitable for *in vitro* experiments although it demonstrates promoter leakage in cell lines and cultured neurons in resting conditions.

The utility of generated plasmids was also tested *in vivo* in mouse hippocampus. For efficient neuron-specific delivery of genetic constructs we produced high-titer recombinant AAV2 viruses. In a couple of weeks after AAV injection, we performed surgical implantation of miniaturized fluorescence microscopes (miniscopes) to monitor calcium activity in specific subset of neurons (“engram”) in real time. Background fluorescence was not detected in hippocampus neither in living cells (GCamp6s), nor in postmortem sections (GCamp6s, mCherry) in the absence of Dox, indicating a strong transcriptional control. Intraperitoneal injection of Dox, followed by the placement of animals into enriched environment (EE) and single-trial fear conditioning training, led to induction of Tet-On 3G system, which resulted in a strong but reversible expression of GCamp6s and mCherry proteins. Our system was also useful for repeated cell labeling during new learning after complete attenuation of fluorescent calcium signal in previously marked cells below the threshold of miniscope detection. Therefore, our preliminary results demonstrate a great potential of the current version of Tet-On 3G system for *in vivo* applications, such as labeling of functional neural networks and recording of cellular activity in real time. For future studies we are planning to expand the capacities of currently used Tet-On 3G system to a level of regulation of functional neural networks.

Acknowledgements

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KNOCKDOWN OF 5-HT1A RECEPTOR SILENCER FREUD-1 IN THE FRONTAL CORTEX AFFECTED THE BEHAVIOR AND THE SEROTONIN SYSTEM IN MICE

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Background

The serotonin (5-HT) system is involved in a variety patterns of behavior. Accordingly, there are a lot regulators of 5-HT system. One of them is silencer Freud-1, that can suppress 5-HT1A receptor expression [1]. Reductions in 5-HT1A receptor expression or activity are observed in patients with anxiety, major depression or suicide victims [2]. However, comprehensive understanding of interaction between 5-HT1A receptor and its repressive transcriptional factor Freud-1, encoding by the *Cc2d1a* gene, is not achieved. Moreover, the contribution of this transcriptional factor in the regulation of the 5-HT system and behavior is still poorly understood.

Aim

Thus, the aim of this study was to investigate the effects of the transcriptional factor Freud-1 knockdown in the frontal cortex on the regulation of normal and depressive-like behavior, as well as brain 5-HT system in mice.

Methods

We have constructed pAAV_H1-2_shRNA-Freud-1 plasmid and carried out gene delivery to induce knockdown of the *Cc2d1a* gene in the cortical neurons in the C57Bl6/J mice. As a control we have injected plasmid encoding a random shRNA with no affinity for the mouse genome in buffer. Locomotor activity, anxiety, exploratory, social and depressive-like behavior were analyzed in open-field (OF), tail suspension (TST), forced swimming (FST) and resident-intruder (RI) tests. Learning and memory were assessed using Morris water maze (MWM) and novel object recognition (NOR) tests. The mRNA levels of *Htr1a*, *Htr2a*, *Htr7*, *Tph2* and *Cc2d1a* genes were assessed by real-time RT-PCR. 5-HT1A, 5-HT2A, 5-HT7, TPH2 and Freud-1 protein levels were analyzed by western blot. Functional activity of 5-HT1A receptor was assessed by hypothermic response to acute administration of agonist 8-OH-DPAT (1 mg/kg i.p.). The data were analyzed by one-way ANOVA. Results of MWM were analyzed using a repeated measure ANOVA. The time spent in the target sector during the retest was compared with the random value (25%) using the t-test.

Results

Administration of AAV-Freud-1 in the frontal cortex resulted in the effective knockdown of Freud-1, both in the mRNA level ($p<0.05$) and protein level ($p<0.001$). According to the role of the Freud-1, we have also found the increasing expression of 5-HT1A receptor in the frontal cortex, both in the mRNA level ($p<0.01$) and protein level ($p=0.06$). On the other hand, there were no significant differences in the 5-HT1A functional activity between experimental and control mice. Additionally, we have observed the trend in the decreasing of mRNA level of *Htr7* gene ($p=0.07$) in the frontal cortex. Any significant changes were no detected in the midbrain both mRNA and protein levels of all studied genes. Silhouette change rate in the FST was increased ($p<0.01$) in *Cc2d1a* knockdown mice, which could reflect antidepressive effect. Furthermore, time of social interaction in RI test was increased ($p<0.01$) in the AAV-Freud-1 group. Also, *Cc2d1a* knockdown failed to produce any changes in the OF, NOR, TST, MWM.

Conclusion

Thus, we have shown for the first time that *Cc2d1a* knockdown in the frontal cortex produced antidepressive effect accompanied by increase in 5-HT1A receptor expression. Our findings demonstrate that Freud-1 may implicated in the regulation of depressive-like behavior through modulation 5-HT1A receptor expression.

Acknowledgements
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ELABORATION OF CONTEXTUAL MEMORY AND FEATURES OF THE PROCESS OF ITS RECONSOLIDATION IN *HELIX*

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Memory is one of the main human cognitive functions. It allows us to recall past events, thoughts, sensations and relationships between them. Memory is the brain's ability to receive, encode, store and retrieve information. The formation of memory occurs in several stages (according to McGaugh's review): short-term, long-term and long-lasting memory. Short-term memory proceeds to be a long-term memory through a phenomenon called consolidation, in which memory can be stored for a long time. Memory consolidation plays a key role in the processes of memory formation and storage, as it determines the coding and duration of storage of traces of memory - engrams. Long-term memory is resistant to the inhibition of protein biosynthesis; however, the consolidation stage requires the expression of genes and the synthesis of new proteins. Consolidated long-term memory can be reorganized as a result of a reminder - presenting one of the components of the learning situation to the trained animal after getting contextually accustomed to that situation. If we inhibit protein synthesis in the animal shortly after presenting a reminder of a previous experience the consolidated memory of this experience will disappear. This process of memory reconsolidating after a reminder is called reconsolidation and also requires protein synthesis.

Associative learning (elaboration of a conditioned reflex) occurs within the context of a large set of sensory information coming from sensory neurons. Interneurons sum up the received signals (integrate the information) and produce the resulting signal, which leads to a reflex response. The signals manifest through neurotransmitter systems, which play important roles in integrative processes in the nervous system. Serotonin (5-HT) has been proved to be the main neurotransmitter that mediates defensive behaviour in terrestrial snails, therefore the role of the serotonergic system in the development of conditioned defensive reflexes in snails is difficult to overestimate. The discovery of the ability of mammalian cells to synthesize the free radical nitric oxide (NO) has stimulated a huge effort by researchers to study the role of NO in all areas of biology and medicine.

Therefore, we conducted a study of the role of 5-HT and NO in learning mechanisms. It was shown that inhibiting the rate-limiting enzyme of serotonin synthesis tryptophan hydroxylase by para-chlorophenylalanine at a dose of 30 mg/kg of weight 3 days before training hinders the elaboration of the conditioned reflex of food aversion in snails and subsequently leads to a decrease in the excitability of the premotor interneurons of the reflex. It was found that NO-synthase inhibitor acceleratesthe elaboration of this conditioned reflexwhile NO donor slowit down and that is also accompanied by changes in the electrical characteristics of the premotor interneurons.

CREATION OF THE ADENO-ASSOCIATED VIRAL VECTOR AAV-CMV-AB42 FOR MODELLING OF ALZHEIMER'S DISEASE *IN VITRO*

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Alzheimer's disease (AD) is one of the most common neurodegenerative disorders, but its cause still remains poorly understood. A characteristic factor is the presence of senile plaques consisting of β-amyloid peptide (Aβ). It is formed from the amyloid precursor protein (APP), which is cleaved by β- and γ-secretases via the amyloidogenic pathway. Since there is no clear therapeutic approach, the study of complex and multifactorial pathogenesis, as well as the trial of new drugs, are the high-priority tasks. For these purposes, animal models are a valuable tool, although they require further improvement.

Aims

The main goal of this research is to create adeno-associated viral vector AAV-CMV-Aβ42 for the modelling of Alzheimer's disease using primary neural cultures from mouse cerebral cortex.

Materials and Methods

In present study, we use the recombinant adeno-associated viral vector (AAV) for delivery of Aβ42 gene. The plasmid vector was originally prepared using standard molecular cloning techniques. An original primer system: Ab_42_BamHI_fw 5′ –ATTGGATCCATGGATGCAGAATTCCGA– 3′ and Ab_42_Agel_rv 5′ –AATACCGGTTTACGCTATGACAACACCG– 3′ was developed to amplify fragment of Aβ42 gene (126 bp). Then we cloned the Aβ42 fragment into AAV- CMV plasmid. Next, the viral vector was assembled in the HEK 293T cell line using the constructed plasmid vector AAV-CMV-Aβ42 and helper plasmids AAV-DJ and pHelper (AAV Helper-Free Packaging System).

The next step was the transduction of HEK293T cell culture and primary neuronal culture to estimate the viral expression. To identify β-amyloid peptide in transduced cultures, immunocytochemical analysis was used. The dynamics of the increase in the expression of Aβ42 mRNA in neuronal cultures of the cerebral cortex obtained from C57Bl/6 and 5xFAD mice srains were studied using real-time PCR (qPCR). Isolation of total RNA was carried out on 3, 7, 12, 17, 21 and 24 days of cultivation. The concentration of nucleic acid in the samples was measured using NanoDrop. The sequences of primer systems qPCR_Ab42_fw 5'-ATGCAGAATTCCGACATGACTCAGGA-3' and qPCR_Ab42_rv 5'-CACCATGAGTCCAATGATTGCACCTT-3' (107 bp); qPCR_Oaz1_fw 5'-AAGGACAGTTTTGCAGCTCTCC-3' and qPCR_Oaz1_rv 5'-TCTGTCCTCACGGTTCTTGGG-3' (93 bp) were developed using the Lasergene PrimerSelect и NCBI Primer-BLAST software. Data processing was carried out using the ΔΔCt method and control samples (total RNA from C57Bl/6, 5xFAD, and 5xFAD (wt) 3 DIV cultures), in which the target gene expression level was set as unit. Normalization was carried out relative to the reference gene encoding ornithine decarboxylase antizim 1 (Oaz1). Further processing was carried out using GraphPad Prism 8.4.3 software.

Results

An adeno-associated virus containing a fragment of the Aβ42 gene provided strong expression in HEK293T cell cultures and primary neuronal cultures of the mouse cerebral cortex. The expression was proved by immunocytochemistry and qPCR methods. According to the primary qPCR data, a short-term increase in expression was observed on 7 and 21 DIV in control neuronal cultures C57Bl/6 and 5xFAD (WT). The bursts are caused by an increase in the synthesis of the amyloid precursor protein during this period, since APP determines the synaptic plasticity and axonal transport in neurons. In 5xFAD (FAD) cultures, the described bursts were absent, most likely due to the presence of APP and PSEN mutant genes. After transduction of C57Bl/6 neuronal cultures with the viral vector AAV-CMV-Aβ42, the expression of β-amyloid mRNA sharply increased on 7 DIV and maintained throughout the experiment.

Conclusions

Thereby it the adeno-associated viral vector containing a fragment of the Aβ42 gene was created. It was shown that transduction of AAV-CMV-Aβ42 leads to a significant increase in the level of Aβ42 mRNA expression in primary cortical neuronal cultures obtained from C57Bl/6 mice strain compared to 5xFAD.

THE OVEREXPRESSION OF TRUNCATED FORM OF TRKB RECEPTOR (TRKB.T1) IN THE HIPPOCAMPUS DIFFERENTIALLY REGULATE THE BEHAVIOR IN DEPRESSIVE AND NON-DEPRESSIVE MICE

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Aims

The diversity of brain-derived neurotrophic factor (BDNF) functions is regulated by the tropomyosin receptor kinase B (TrkB) and its isoforms. One of them is a truncated form - TrkB.T1. To date, a large number of TrkB.T1 functions have been identified [1], but their role in the regulation of various forms of behavior remains unclear. Both, knockdown [2] and overexpression [3] of TrkB.T1 throughout the forebrain in mice affected anxiety and aggressive behavior as well as spatial learning and memory. However, these studies did not consider the contribution of individual brain structures to the regulation of a particular behavior. In addition, in these studies, the contribution of astrocytic and neuronal TrkB.T1 was not distinguished. Another question that needs to be addressed is how TrkB.T1 implicated in the pathogenesis of mood disorders? Available data are scarce and contradictory. So, the aim of our study was the investigation of the effects of TrkB.T1 overexpression in the hippocampal neurons on behavior of mice with genetically defined depressive-like behavior as well as normal animals.

Methods

We have constructed the pAAV_Syn_TrkB.T1-EGFP plasmid and used AAV-mediated gene delivery to induce overexpression of TrkB.T1 in the hippocampal neurons of C57Bl6/J (non-depressive) and ASC (Antidepressant Sensitive Cataleptics) mice characterized genetically defined depressive-like behavior [4]. Locomotor activity, anxiety, exploratory, aggressive/social and depressive-like behavior were analyzed in open-field (OF), elevated plus-maze (EPM), resident-intruder (RI) and tail-suspension (TST) tests.

Results

Administration of AAV-TrkB.T1 produced overexpression of TrkB.T1 in the hippocampus of C57Bl6/J and ASC mice ($p<0.001$). We have revealed that in C57Bl6/J mice TrkB.T1 overexpression significantly increased ($p<0.05$) the number and duration of rearings without affecting locomotor activity in the OF test. The number and duration of groomings were decreased ($p<0.05$) while the latent time of first grooming was substantially increased ($p<0.05$) in C57Bl6/J mice of AAV-TrkB.T1 group. In contrast, TrkB.T1 overexpression in ASC mice produced decrease in locomotor activity ($p<0.01$) and number of rearings ($p<0.01$), while increased ($p<0.01$) duration of groomings. In the EPM both explored area and the time in the center of arena as well as number of looks down from the edge of arena were increased ($p<0.01$) in AAV-TrkB.T1 group of C57Bl6/J mice. In ASC mice we have observed a decrease in locomotor activity ($p<0.01$) and the number of peeks from the closed arm ($p<0.05$) in the EPM only in animals with TrkB.T1 overexpression. While in the C57Bl6/J mice overexpression of TrkB.T1 failed to affect aggressive and social behavior in RI test, in ASC mice we have revealed a dramatic decrease in the number ($p<0.01$), duration ($p<0.01$) and latency ($p<0.001$) of aggressive encounters and subsequent increase in duration of social non-aggressive contacts ($p<0.05$). At the same time TrkB.T1 overexpression failed to produce any changes in TST in both C57Bl6/J and ASC mice. Together these data indicate decrease in anxiety and increase in exploratory behavior of experimental animals in C57Bl6/J line, but decrease in locomotor activity and exploratory behavior with slight increase in anxiety in AAV-TrkB.T1

group of ASC mice. At the same time anti-aggressive and prosocial effects of TrkB.T1 overexpression were observed only in ASC mice. Depressive-like behavior was not affected by overexpression TrkB.T1 in both investigated lines.

Conclusions

Our results show that the functions of neuronal TrkB.T1 are not universal throughout the forebrain and may largely depend on the specific brain structure. This probably explains the contribution of TrkB.T1 to the regulation of behavior at the level of individual patterns. Moreover, we have shown for the first time that neuronal TrkB.T1 in the hippocampus may be sufficient for production of strong anti-aggressive effect but only in animals with depressive-like phenotype. Together with data on opposite action of TrkB.T1 overexpression on anxiety and exploratory behavior in depressive and non-depressive animals these findings indicate that TrkB.T1 functioning may be changed under psychopathology.

Acknowledgements

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MOLECULAR AND CELLULAR MECHANISMS OF POSTTRAUMATIC STRESS DISORDER

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Aims

The mechanisms of post-traumatic stress disorder (PTSD) have attracted increasing attention in recent years. However, despite the great success in the study of PTSD at the behavioral, psychological and physiological level in humans, as well as large number animal models of PTSD, the phenomenon of PTSD remains largely incomprehensible in theoretical terms. The aim of this project is to establish the neural basis for the pathological stability of traumatic memory that formed when encountering a stressful situation leading to the development of PTSD and to study the differences between the mechanisms of normal and traumatic memory formation at the neural level.

Methods and results

First, we subjected mice to single traumatic experience and studied the dependence of PTSD development on protein synthesis during the consolidation and reconsolidation of traumatic memory. Mice injected with protein synthesis inhibitor cycloheximide (90 mg/kg, i.p.) 30 min before PTSD induction retained contextual

associative memory but did not show a pronounced contextual fear. The results of elevated plus maze test suggests that the protein synthesis inhibition during the consolidation of traumatic memory can not only prevent the development of PTSD, but also disrupt the natural defensive behavior of animals, making them less anxious than control mice who had no previous negative experience.

After that, we showed that protein synthesis inhibition during the reconsolidation of traumatic memory almost completely abolish non-specific symptoms of trauma in mice, such as increased sensitization, fear generalization and anxiety. At the same time, however, cycloheximide injection during reminder did not affect the associative fear memory. These results show a dissociation between associative and nonassociative consequences of a traumatic experience in terms of their sensitivity to impairment during memory retrieval.

We also studied the dependence of PTSD development on de novo methylation processes. Methyltransferase inhibitors 5-AZA and RG108 injection (0.5 mg/kg, i.p.) 30 min before traumatic episode reduced PTSD symptoms in mice: it decreased the level of conditioned fear and affected the level of behavioral sensitization and anxiety, but not the generalization. The inhibition of methylation processes during the reconsolidation of traumatic memory did not affect the symptoms of PTSD according to our data.

We analyzed the c-Fos activity of the brain in the formation of normal contextual fear memory (FC) and traumatic memory in order to answer the second question of this project. The formation of traumatic memory was accompanied by activation of a pattern of brain areas similar to that activated during formation of FC memory. However, in PTSD the activity of amygdala, prelimbic cortex and dentate gyrus was considerably more pronounced.

Conclusions

These results show important differences between normal and traumatic forms of memory at the time of their formation. In addition, we hypothesize that increased activation of the amygdala and prefrontal cortex in PTSD may be associated with pathological persistence of traumatic memory.

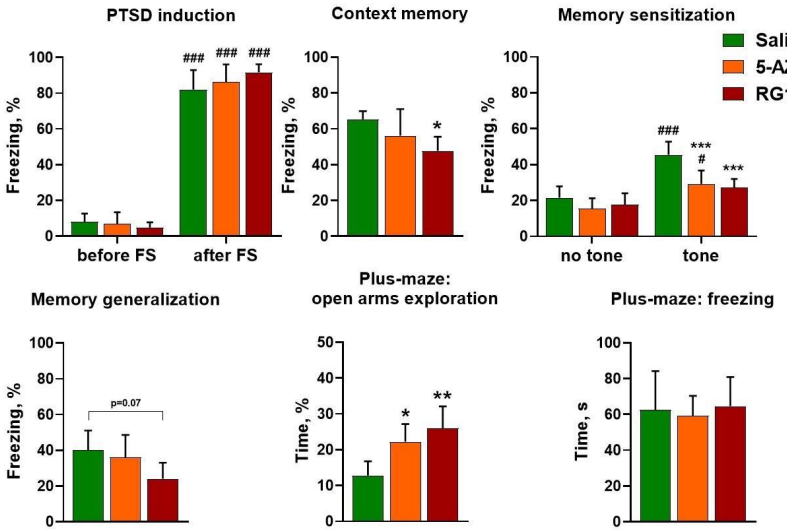

Fig.1. PTSD development prevention by methyltransferase inhibitors 5-AZA and RG108 injection before traumatic events. Behavioral tests data. *– p<0.05, ** – p<0.01, *** – p<0.001, compared to Saline, Tukey's HSD; ### – p<0.0001, compared to freezing level in the same group in different time interval, Sidak test

Acknowledgements

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ON THE ROLE OF SEROTONIN 5-HT1A RECEPTOR TRANSCRIPTIONAL FACTOR CC2D1A/FREUD-1 IN THE BRAIN 5-HT AND BDNF SYSTEMS CROSS-TALK AND BEHAVIORAL PLASTICITY

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Background

Serotonin 5-HT1A receptor is one of the most abundant and widely distributed brain serotonin (5-HT) receptors playing a major role in the modulation of emotions and behavior. In 2000, in the promoter of the gene encoding 5-HT1A receptor, a binding site (DRE element) for a selective repressor suppressing the receptor gene expression was detected [1]. Later, the transcriptional factor Freud-1 which binds to the DRE element in the promoter of the 5-HT1A receptor gene leading to the suppression of the receptor gene expression in the brain was identified [2]. It is known that changes in the expression of the 5-HT1A gene can differentially affect pre- and postsynaptic 5-HT1A receptors and, therefore, the functional activity of the brain 5-HT system. Taking into account the role of the 5- HT1A receptor in autoregulation of the brain 5-HT system function [3] the transcriptional factors of the 5-HT1A receptor gene can be considered as potential regulators of 5-HT-dependent behavior.

In recent decades a lot of data indicating close relation between brain 5-HT and brain-derived neurotrophic factor (BDNF) systems were obtained. The cross-talk between these two brain systems seem to be crucially important for their functioning and for regulation of different physiological processes [4,5].

Aim

The aim of the present study was the investigation of the effect of the Cc2d1a gene expression suppression in the hippocampus using adeno-associated viral (AAV) particles carrying the plasmid encoding small hairpin RNA (shRNA) against Cc2d1a gene on (i) behavior in the open field test (OF), forced swim test (FST) and Morris water maze (MWM), (ii) mRNA and protein levels of Cc2d1a, Htr1a, Htr2a, Htr7, Bdnf , Ntrk2 (TrkB receptor gene), Ngfr (p75NTR receptor gene), Creb, RelA (encoding subunit P65 of NF kappa B factor), Nfkb1 (encoding subunit P50 of NF kappa B factor), cFos (as a marker of neuronal activity), and (iii) 5-HT, 5-hydroxyindoleacetic acid (5-HIAA) levels and 5-HIAA/5-HT ratio in the hippocampus of C57BL/6J mice.

Methods

We have constructed pAAV_H1-2_shRNA-Freud-1_Syn_EGFP plasmid and carried out gene delivery to induce knockdown of the Cc2d1a gene in the hippocampal neurons in the C57Bl6/J mice using AAV. Locomotor activity, depressive-like behavior was analyzed in open-field, forced swim tests. Learning and memory were assessed using Morris water maze test. The mRNA levels of genes were assessed by real-time RT-PCR. Protein levels were analyzed by western blot. The levels of monoamines were detected by HPLC. Functional activity of 5-HT1A receptor was assessed by hypothermic response to acute administration of agonist 8-OH-DPAT (1 mg/kg i.p.). The data were analyzed by one-way ANOVA. Results of MWM were analyzed using repeated measure ANOVA. The time spent in the target sector during the retest was compared with the random value (25%) using the t-test.

Results

AAV particles carrying pAAV_H1-2_shRNA-Freud-1_Syn_EGFP encoding shRNA against mouse Cc2d1a gene produced an antidepressant effect in the forced swim test five weeks after administration. However, it caused disturbance in spatial-temporal memory assessed in Morris water maze. pAAV_H1-2_shRNA-Freud-1_Syn_EGFP resulted in the decrease in Cc2d1a gene mRNA level and Freud-1 protein. Furthermore, Cc2d1a gene knockdown increased 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) levels, but not 5-HIAA/5-HT ratio. Cc2d1a gene knockdown failed to affect mRNA and protein levels of Htr1a gene, however, it produced a decrease in the 5-HT1A receptor functional response. At the same time, Cc2d1a gene knockdown decreased Creb mRNA and phosphorylated CREB protein level, and increased cFos mRNA level. Suppression

of the Cc2d1a gene expression increased expression of BDNF precursor proBDNF protein that is known to play a crucial role in the neuroplasticity.

Conclusion

This work showed for the first time that partial knockdown of the Cc2d1a in the hippocampus produces the antidepressant effect accompanied by significant changes in both brain 5-HT and BDNF systems. At the same time, Freud-1 knockdown decreased the 5-HT1A receptor functional activity and increased 5-HT and 5-HIAA levels in the hippocampus. Our data suggest that BDNF system and transcriptional factor CREB are also involved in the mechanism underlying Freud-1-dependent antidepressant effect. Moreover, Freud-1 is able to affect BDNF system functioning that can play a significant role in the pathogenesis of different mental disorders and depression.

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EFFECTS OF THE SEROTONIN 5-HT7 RECEPTOR OVEREXPRESSION IN THE RAPHE NUCLEI AREA ON DEPRESSIVE-LIKE BEHAVIOR AND BRAIN 5-HT SYSTEM IN MICE

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Heterodimerization between 5-HT7 and 5-HT1A receptors is known to play an important role in the mechanism underlying depression and antidepressant-drug action. It was suggested that the shift of 5-HT1A / 5-HT1A homo- and 5-HT1A / 5-HT7 heterodimers ratio in presynaptic neurons towards homodimers is one of the reasons of depression. Consequently, elevation of 5-HT7 receptor number in presynaptic terminals might restore physiological homo- / heterodimers ratio resulting to antidepressant effect. So, the aim of the study was to investigate the effects of 5-HT7 receptor overexpression in the midbrain raphe nuclei area on depressive-like behavior and on the brain 5-HT system in C57Bl/6J mice and genetically predisposed to depressive-like behavior ASC (Antidepressant Sensitive Cataleptics) mice.

The experiments were carried out on adult males of C57Bl/6J mice and genetically predisposed to depressive-like behavior ASC mice. Adeno-associated viral particles carrying pAAV_Syn_HTR7-EGFP plasmid, providing overexpression of Htr7 gene, were administered in the raphe nuclei area of the midbrain using stereotactic frame. Control mice were treated with AAVs carrying pAAV_Syn-EGFP plasmid. Behavior was studied in the open field and forced-swim test. The levels of Htr1a, Htr7, Slc6a4, Tph-2 genes expression were evaluated by quantitative real-time PCR. 5-HT1A, 5-HT7, TpH2 and 5-HTT protein levels were assessed by Western-Blotting. 5-HT and 5-HIAA levels were estimated with HPLC The mean values were compared using Student t-test.

In the current study we confirmed this idea showing that 5-HT7 receptor overexpression in the midbrain raphe nuclei area produced antidepressive effect both in C57BL/6J and genetically predisposed to depressive-

like behavior ASC mice. These changes were accompanied by expected 5-HT7 receptor overexpression in the midbrain in both mouse strains as well as by elevation of 5-HT7 receptor mRNA level in the frontal cortex of C57Bl/6J and its reduction in the hippocampus of ASC mice. To further prove 5-HT7 receptor overexpression we showed the presence of 5-HT7-EGFP protein in the midbrain of both investigated mouse strains. Importantly that 5-HT7 receptor overexpression resulted in reduction of 5-HT1A receptor level in the membrane protein fraction from midbrain samples of C57Bl/6J but not ASC mice. 5-HT7 receptor overexpression caused an increase of 5-HIAA/5-HT ratio in the midbrain of C57Bl/6J and in all investigated brain structures of ASC mice.

Thus, we showed that 5-HT7 receptor overexpression in the midbrain raphe nuclei area causes antidepressive effect and affects brain 5-HT system both in “nondepressive” C57Bl/6J and “depressive” ASC mice. Obtained results are in agreement with our suggestion on the 5-HT1A/5-HT7 heterodimerization role in the regulation of depressive-like behavior.

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TRAUMATIC BRAIN INJURY THERAPY USING 3D BIOENGINEERING CONSTRUCTS

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Traumatic brain injury (TBI) is a dynamic process involving a large number of pathological cellular pathways [1]. Despite active research into substances that could promote the regeneration of nerve tissue, at present, complete recovery from trauma is difficult to achieve.

Normalization of the functional state of damaged brain tissue by stimulating cell growth is much more effective than approaches associated with the use of replacement structures. Therefore, currently a promising method is the use of bioengineering structures (scaffolds). They represent 3D bioactive matrices for neurotransplantation containing various biological compounds that accelerate the repair processes of nerve tissue, including neurotrophins and components of the brain's extracellular matrix (hyaluronic acid).

Therapy of brain tissue with bioengineered constructs has advantages over single-dose pharmacotherapy: transplants can anatomically reconstruct the damaged brain and activate hidden pathways that exist in the brain, or stimulate new ones after injury, and then help improve the functional activity of the brain [2].

The aim of the scientific research is to study the influence of various variations of bioengineering structures (scaffolds) on the processes of brain tissue regeneration in the simulation of TBI, as well as their modernization.

During the study, males of the C57Bl / 6 line were used. TBI was simulated by the method of free fall of a load onto an open area of the brain. On the 7th day, scaffolds are transplanted to the experimental groups, the control group is observed with TBI. In early research, we arrived at the choice of a specific chemical composition for the scaffold. The use of a material based on hyaluronic acid, with a high content of riboflavin and synthetic substances, stimulates regenerative processes in the brain after simulating an open traumatic brain injury.

In our study, considering previous experiments, we considered two types of necessary therapy: one of the types of therapy was the addition of neurotrophic factors (BDNF and GDNF), which should enhance the effect of restoring the morphological characteristics of brain tissue; the second type of therapy was the introduction of the osmodiuretic furosemide, which should reduce the vasogenic cerebral edema that occurs after TBI, which did not allow full regeneration of the nervous tissue.

The experiment was designed in such a way that the dynamics of the development of the TBI focus, both with and without a matrix, was monitored. On the seventh day of the post-traumatic period, using magnetic resonance imaging and histological samples, the reaction of the nervous tissue to the trauma and to the construct was examined. Behavioral and physiological screening of animals was also carried out.

It has been shown that the use of a material based on hyaluronic acid, with a high content of riboflavin and synthetic substances, stimulates regenerative processes in the brain after modeling an open traumatic brain

injury. The addition of neurotrophic factors, at the correct concentration, will only enhance the effect of restoring the morphological characteristics of the brain tissue and cognitive functions. The scaffold with the introduction of the GDNF stood out especially. When using an osmodiuretic, a decrease in cytotoxic edema was shown, in contrast to the TBI group, by 10-15%. This confirms the need for additional pharmacotherapy when using the scaffold. In the future, the use of a combined therapeutic technique will allow considering the possibility of cell regeneration with full restoration of the cognitive functions of the brain.

Acknowledgements

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THE DIVERSITY OF GDNF AND ITS ROLE IN THE REGENERATIVE MEDICINE OF THE HUMAN NERVOUS SYSTEM

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The lack of effective treatments for neurodegenerative diseases provokes looking for new approaches, including cellular technologies. They are developing to increase viability of neurons in the affected area and stimulate neural differentiation of progenitor cells to replenish neurons in the area of their death using transgenic cell cultures. GDNF is in priority position for application as neuroprotector and inducer of neural differentiation of progenitor / stem cells. Therefore, it is important to understand which isoforms of the factor are acceptable for cell therapy. In human GDNF gene yields at least two mRNAs, which differ in size of pro-region. It was suggested that one of the GDNF variants is permanently expressed, and it is required for interactions between nerve cells under normal conditions, while the other (with smaller pro-region size) is secreted and required to stimulate recovery processes during neuronal death. We have shown that deletion of the pre- and pro- regions in the chimeric protein GDNF/GFP increases the neuroprotective properties of the factor. The mGDNF / GFP had enhanced neuro-inductive properties, which was confirmed for in vitro models of rat and PC12 line embryonic spinal ganglia. In vivo, mGDNF/GFP was able to maintain viability of dopaminergic neurons when injected into the brains of model animals with Parkinson's disease, and significantly protected them from the effects of the pro-neurotoxin MPTP. Upon uptake of transgenic mammalian cells producing mGDNF (with no GFP), the factor is unstable. We focused on the fact that several repeated short RNAs for GDNF are found. Probably, in some cases in cells a process can yield not the complete mGDNF, but as a result of alternative splicing mini-factors are produced during mass death of neurons, and probably they are required for restoration of cellular neuronal pool. We have cloned some variants of short-sequences of mGDNF, and analyzed them for neuroinductive properties. One of DjGDNF mini-factor is able to stimulate neuronal differentiation of progenitor cells, and can be considered as a promising molecule for translation into therapy of neurodegenerative diseases.

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HYALURONIDASE-DEPENDENT CHANGES OF ADAR2 IN MOUSE HIPPOCAMPAL CELL CULTURES

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Extracellular brain matrix plays pivotal role in CNS function. Alterations to the ECM may occur after neural injury (for example, in multiple sclerosis, spinal cord injury or Alzheimer's disease) and can have drastic consequences such epilepsy. Epilepsy usually caused by excessive influx of Ca^{2+} ions through (Ca2+)-permeable channels, such as AMPA receptors which may, in certain circumstances, contribute to normal synaptic plasticity or to seizures. AMPA receptors are Ca2+-permeable if they lack the GluA2 subunit or if GluA2 is unedited at a single nucleic acid, known as the Q/R site. Regulation of this process is carried out by special nuclear enzyme Adenosine deaminase acting on RNA 2 (ADAR2). That's why investigation of this enzyme may be useful to study possible role in mechanism of epileptogenesis.

Aim of the present study was to investigate changes of localization, protein and gene expression changes of ADAR2 after 2 day of enzymatic digestion of hyaluronic acid in mouse hippocampal cultures.

Methods

C57BL/6J mice were used to prepare hippocampal cell culture. Hyaluronic acid, were removed by application of 75U/ml hyaluronidase (Sigma-Aldrich, H3506) at the DIV 17. The method of immunocytochemistry was applied for the study of localization of ADAR2 in the neurons. To investigate gene expression changes Real-time PCR method were used with CFX 96 (BioRad) instrument. TaqMan Gene Expression Assay (Hs00953730_m1, Thermo Fischer) was used. Gene expression of ADAR2 was normalized against such housekeeping genes as GAPDH and Beta-Actin and measured by ΔΔCt method.

To assess the change in protein level, the Western blotting method was used. Before starting the analysis, the concentration of total protein in the samples was leveled. Concentration measurements were carried out on a Nanodrop-1000, Thermo, using a BCA-kit. Denaturating electrophoresis with subsequent transfer of proteins to a PVDF membrane was performed using an electrophoresis chamber and a power supply of (Bio-Rad). The results were detected using antibodies to ADAR2 (Abcam). Actin was used to normalize the amount of protein in samples.
Separate isolation of the nuclear and cytoplasmic fraction of the hippocampal cultures was carried out according to the protocol of ThermoFisher Scientific
(https://www.thermofisher.com/ru/ru/home/references/protocols/cell-and-tissue-analysis/elisa-protocol/elisa-sample-preparation-protocols/nuclear-extraction-method)

Results

During this study we found mislocalization of ADAR2 in group with destruction of hyaluronic acid whereas in vehicle and intact group ADAR2 localized mainly in nuclei.

According to real-time pcr data there is increasing of ADAR2 gene expression (1.69 fold) after 2 days in response to hyaluronan destruction in comparison with intact group. Western blot analysis showed increasing protein content of ADAR2 enzyme in group with hyaluronidase application in nuclear fraction, whereas cytoplasmic concentration remained constant. At the same time protein expression of GluA2 subunit decreased in group with hyaluronidase addition.

Conclusions

According to data received decreased protein concentration of GluA2 may shift balance of excitation/inhibition because decresing concentration of GluA2 cause elevated Ca^{2+}-permeability that can be harmful for hippocampal cultures. This event can cause compensatory elevation of ADAR2 gene and protein expression changes to facilitate RNA-editing of Ca-impermeable GluA2 subunits and retain such equilibrium.

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NEURONAL ACTIVITY IN HIPPOCAMPUS OF FREELY MOVING MICE IS AFFECTED BY HDAC INHIBITOR SODIUM BUTYRATE

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Long-term memory consolidation is a complex multi-stage process with gene expression regulation being one of the crucial steps. Epigenetic modifications, such as histone acetylation, have been intensely studied as the potential mechanisms of gene expression regulation during memory maintenance. It was shown previously that rising levels of histone acetylation by inhibition of hystondeacetylases (HDACs) enhances long-term potentiation in hippocampus slices *in vitro* as well as improves long-term memory in context fear conditioning learning [1]. Similar facilitation of long-term potentiation after the HDAC inhibition was reported in several studies [2, 3]. However, the research on histone acetylation as a mechanism of neuronal plasticity has been made mostly in brain slices *in vitro*. The effects of altered hystone acetylation levels on neuronal activity in living and awake brain still remain unknown. The goal of our work was to investigate the effects of HDAC inhibitor sodium butyrate (NaB) on neuronal activity in hippocampus in freely moving mice.

We have used miniature head-mounted microscopes – miniscopes (miniscope.org, UCLA) – to perform calcium imaging recordings of neuronal activity in hippocampal CA1 area. Experimental animals underwent a three-stage surgery to be prepared for behavioral test. First, we have transduced neurons with GCamp6s calcium sensor by a stereotaxic injection of the AAV-based virus vector into CA1. Second, we have implanted a GRIN lens to make optical path from hippocamus to head-mounted miniscope. Third, the base plate for miniscope attachment was installed on mouse skull.

Before behavioral tests, we handled mice with miniscope attached for three days. At the first day of experiment mice were placed into small open field with two unfamiliar objects in the middle for 5 minutes. Synchronized recordings of mouse behavior and neuronal calcium signal were made in parallel. Just after the end of the trial we have injected mice with either NaB (1.2g/kg, N=3) or saline (N=3) and returned them to the home cage. Two 5-min recordings of neuronal activity were made in the home cage 45 and 90 min after the trial. 24 hours later mice were placed in the same trial context but with one old and one new object, and neuronal activity was recorded again.

Data processing was performed using the MIN1PIPE software [4]. Analysis pipeline included automatic selection of ROIs with high fluorescent signal, mapping of the corresponding neuronal cell bodies and extraction of neuronal activity signal from noise. Matching unique neurons throughout the consecutive recordings was made by CellReg software [5].

First, we have counted the total number of active neurons after first trial followed by NaB or saline injection. In control mice the active cells' count increased in both time points 45 and 90 min after injection. The NaB-injected mice demonstrated a prominent decrease of the number of active neurons at 45 min time point with a slow return to initial level 90 min later.

Next, we have analyzed dynamics of the mean calcium events frequency in active neurons in two groups. Mean frequency has been slowly increasing in saline-injected mice during the repetitive recordings. At the same time, in NaB-injected mice the frequency was decreased at 45- and 90-min time points and returned to initial values 24 hours later.

Matching individual neurons in repetitive trials revealed certain patterns of neuronal activation.

General number of neurons being active after injection was higher in control than in NaB mice. However, the number of neurons being active only in experimental context (both in initial learning and 24h test trials) was higher in NaB group. Moreover, the dynamics of calcium events frequency was similar in both saline and NaB groups in neurons that was active during initial learning and no less than 90 min later: injection of either saline or NaB was equally followed by increase in frequency at least for 90 minutes.

The results taken together suggest that NaB affects activity of the hippocampal neurons depending on their previous state. Initially active neurons remain active after NaB injecting while in other neurons the probability of activation and mean frequency of calcium events become lower. One may speculate that NaB selectively downregulates neurons not associated with new experience gained during the learning trial.

Acknowledgements

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STUDY OF HIPPOCAMPAL NEURONAL ACTIVITY IN FREELY MOVING MICE DURING CONTEXT FEAR CONDITIONING TASK

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According to the modern conceptions of long-term memory, it may be stored in a subpopulation of connected neurons being active at the time of memory formation – so called engram [1]. Physiological activity of these cells correlates with specific episodes of memory acquisition and their activation triggers or, on the contrary, suppresses reactivation of the specific memory trace [2]. Investigation of the mechanisms of engram formation is one of the most important directions of fundamental research of memory and learning. Research of the temporal dynamics of such neuronal subpopulations' activity and connectivity became possible after invention of *in vivo* fluorescent calcium imaging techniques including miniature head-mounted fluorescent microscopes – miniscopes – allowing researcher to record multiple neurons at once in awake, freely-moving animals.

Our study main goal was to investigate dynamics of calcium activity in hippocampal neurons during contextual aversive memory formation and reactivation. Animals were learned in a widely used behavioral model of context fear conditioning (cFC).

At first, we have assembled custom-made cFC setup and tested the intact mice (without miniscopes) performance. Experimental protocol was as follows: 120s of free exploration of the chamber, 2s of electrical footshock (intensity varied in different groups – 0 in control, 0.30 mA, 0.45 mA and 0.60 mA), 30s of exploration. 24h and 48h after learning mice were placed in the chamber for 3min to test the memory.

Next, we have trained mice stereotaxically injected 3 weeks earlier with vector AAV-CAG-GCamp6s and miniscopes implanted. Calcium sensor GCamp6s was expressed in CA1 neurons, where the miniscope GRIN lens was implanted. Animal behavior was recorded synchronously with neuronal fluorescent calcium signal. 24 hours later the test trial was made with parallel recording of behavior and neuronal activity. Fluorescent signal analysis was made using MIN1PIPE software, cell matching in consecutive trials – with CellReg.

In the first set of experiments (intact mice) all animals have actively explored new context inside the FC chamber with no signs of fear (total freezing time less than 2%). After the footshock all groups except control have demonstrated transient freezing episodes (less than 10% at average). 24 hours later, the trained mice (0.45 mA and 0.60 mA) have shown statistically significant increase in freezing duration in comparison to control ones (control – 3%; 0.45 mA – 21.6%, p = 0.02; 0.60 mA – 20%, p = 0.04; one-way ANOVA with Tukey post-hoc). During second test the mice reinforced with 0,6 mA have shown significantly higher percent of freezing than other trained mice (p = 0.04 and p=0.009, respectively, one-way ANOVA with Tukey post-hoc. Thus, we chose 0,6 mA footshock for further experiments.

In the second set of experiments (with miniscopes) mice were trained with 0.6 mA footshock, total freezing time during test trial 24h later was 29.3% of the trial length. Recordings of individual neurons in CA1 hippocampal area during learning and testing were analyzed, number of active neurons and frequency of calcium spikes were counted. Next, calcium imaging data was compared with behavior recordings to distinguish neurons being active at different stages of learning (before, during and after footshock). Activity of the neurons in these subgroups during test trial was analyzed.

At the moment we have assembled and tested open-source miniscope and custom-made fear conditioning chamber, selected optimal footshock intensity in the set of experiments and revealed temporal dynamics of CA1 hippocampal neuronal activity during learning and retrieval of long-term memory.

Acknowledgments

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PHENOTYPICAL CHARACTERISTIC OF THE MUTANT MICE STRAIN S5-1 SHOWING EPILEPTIFORM ACTIVITY

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Epilepsy is a chronic neuralgic disorder characterized by spontaneous repetitive seizures accompanied by various disorders of motor, sensory, autonomic and mental functions caused by excessive electrical activity of neurons. The understanding of the mechanisms controlling epileptogenesis can be developed by identifying and then describing mutations causing this pathology.

The aim of the study is to characterize the mutant mice strain S5-1, which shows induced epileptiform activity in response to audiogenic stimulation.

Mutant mice strains were obtained by induced chemical mutagenesis using N-ethyl-N-nitrosourea (ENU). During the study 3 series of ENU-injections at a dose of 90 mg / kg were given to 29 male mice. The identification and selection of mouse mutants with an increased tendency to epileptic seizures was carried out on the twenty-first day after birth (P20) using the Krushinsky scale, taking into account the intensity of audiogenic seizures. The creation of strains with a recessive mutation was carried out by selecting animals showing the aberrant phenotype for the second time. The inheritance of the aberrant phenotype was confirmed in the G5 generation. As a result of screening 60 mice strains for sensitivity to audiogenic stimulation, 12 strains showing the signs of epileptiform activity were identified. For further work, the S5-1 group was chosen, since the frequency of the aberrant phenotype in the offspring (G3) was higher in comparison with the other groups. To characterize the obtained epileptic srains, basic behavioral phenotyping was carried out, including the assessment of memory, learning ability, motor-motor reactions and emotional status. *In vitro* experiments were also carried

out to assess spontaneous calcium activity using primary neuronal cultures of the cerebral cortex isolated from newborn mice. *In vitro* experiments were performed on acute hippocampal slices isolated from 1.5-month-old mice. The perforant path was activated by electrical stimulation of the CA3 hippocampal region with the further registration of presynaptic and postsynaptic field potentials in the CA1 and CA2 regions. The studied parameters were the rise rate of the response (Slope) and the ratio of the response amplitudes. It has been hypothesized that changes in the hippocampal networks can occur at the level of individual neural micronets. In this regard, the registration of field potentials in 4 microregions of the hippocampus, located in the layers of the stratum pyramidale and stratum radiatum in CA1 and CA2 regions, was investigated. In particular, experiments were carried out to register the calcium activity of astrocytes in hippocampal slices. For *in vivo* labeling of glial cells, the astrocytic marker Sulforhodamine 101 (SR) and the Ca^{2+} indicator Oregon Green 488 BAPTA-1 AM were used.

The complex of behavioral studies of S5-1 mice revealed a higher intensity of the acoustic startle response compared to the control hybrid animal group. Also, the open field tests showed, that according to the average distance traveled, the motor activity of mice from S5-1 strain was higher than in the control group, but the level of anxiety was reduced and was determined by a smaller number of rears. When assessing cognitive functions using the CPAR test, mutant individuals showed a high learning ability. *In vitro* experiments revealed an increase in the frequency of spontaneous calcium events in primary cell cultures of the cerebral cortex isolated from S5-1 mice. After conducting *in vitro* experiments to assess synaptic transmission in hippocampal slices based on recording field excitatory postsynaptic potentials, micronets of the hippocampus with a significant decrease in synaptic transmission were found in animals with epileptiform behavioral activity. The location of these micronets indicates impairments in synaptic transmission in the apical dendrites of the pyramidal cells of the hippocampus. In particular, a significant decrease in long-term synaptic plasticity was found in animals with epileptiform activity compared with the control group. The functional activity of astrocytes in hippocampal slices was investigated. There was a statistically significant decrease in the frequency and duration of events in the group with epileptiform activity compared with the control group. There is a significant increase in the number of astrocytes in the epileptic group, which indicates changes in the astrocyte functioning.

Based on the data, it is possible to suggest a probable mechanism for altering synaptic transmission and astrocyte functioning in the new mutant mice strain S5-1. As a result of point mutations, caused by the effect of a mutagen on a DNA molecule, a number of pathologies develop. Thus, one of the pathologies is a violation of the cytoarchitecture of the cerebral cortex. Soon, this leads to an indirect change in the subcortical structures, in particular in the hippocampus, as well as to the development of audiogenic seizures. As a result, there is an impaired synaptic transmission, i.e. decreased synaptic activity. This probably leads to dysfunction of astrocytes, namely, to a decrease in functional activity. Astrogliosis also appears, as a common sign of neurodegenerative diseases, including epilepsy.

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OPTOGENETIC APPROACHES TO CONTROL OF ASTROGLIA-DRIVEN BRAIN PLASTICITY

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Aims

Alzheimer's disease (AD) is characterized by progressive neurodegeneration associated with aberrant brain plasticity. Complex pathogenesis of AD includes impairment of astroglial functional activity resulting in loss of astrocyte-neuron metabolic coupling and gliovascular control, development of reactive gliosis and neuroinflammation [1, 2]. Astrocytes could be considered as an attractive target for regulating neuronal survival, synaptic plasticity, neurogenesis and neuroinflammation. Particularly, astroglial cells may affect recruitment and differentiation of stem/progenitor cells as well as angiogenic properties of brain microvessel endothelial cells via lactate production or release of mitochondria [3-6]. The aim of the study was to find out how optogenetically-controlled local microenvironment may affect the neurogenic potential of neural stem cells and neural progenitor cells (NSCs and NPCs, respectively) due to modified metabolic activity of astrocytes in the Alzheimer's type neurodegeneration.

Methods

We used AD mice models (5xFAD mice model, intrahippocampal injection and local application of Aβ1-42 in vivo and in vitro), protocols for establishment of neurovascular unit (NVU) and neurogenic niche (NN) in vitro models, immunostaing protocols for the assessment of expression profile of proteins of interest, optogenetic modulation of astroglial cells (GFAP-ChR2-mKate vectors were kindly provided by Prof. Sergey A. Kasparov, University of Kaliningrad, Russia, University of Bristol, UK), analysis of cells proliferative activity in vitro (XCelligence protocol), brain microdialysis, and spectrofluorimetry.

Results

Hippocampal astrocytes in experimental AD are characterized by the ability to release mitochondria into the extracellular space in vitro, this process is blocked by reduced activity of astroglial NAD+-glycohydrolase/CD38, inhibitors of glycolysis and F-actin remodeling. Mitochondria present in the extracellular space in experimental AD are characterized by a hyperpolarized state, which is confirmed by the presence of glucose hypometabolism and the development of mitochondrial dysfunction, with the acquisition of mitochondrial division processes over their fusion. Toxic effect of Aβ leads to an imbalance in the expression of fusion and fission proteins (MFN1, MFN2, DRP1) in astrocytes. We detected increase in the expression levels of CD38, Cx43 in cells of neuronal, astroglial and endothelial origin in the hippocampus of animals with experimental AD in vivo as well as in the in vitro NN model.

Progression of neurodegeneration is accompanied by suppression of neurogenesis, aberrant expression of NAD+-metabolizing ectoenzymes, and development of NLRP3-mediated neuroinflammation in vivo. In the in vitro model of NN, we found that optogenetic activation of niche astrocytes resulted in stimulation of NSCs/NPCs proliferation (induction of GFAP+(-)+Nestin+PCNA++phenotype) and significant changes in the expression of NAD+-metabolizing or associated molecules (CD38, CD157, Cx43). Stimulation of SGZ niche astrocytes partially restored neurogenic potential of NSCs/NPCs affected by Aβ in vitro.

Conclusions

Compromised neurogenic activity in experimental AD is associated with altered local NAD+ metabolism, mitochondria dysfunction in the cells of NVU/BBB, and development of neuroinflammation. Optogenetic stimulation of niche astrocytes affects NSCs/NPCs proliferation and local microenvironment. CD38-expressing astrocytes could be considered as mitochondrial donor cells for neurons and brain mcirovessel endothelial cells in Alzheimer's type neurodegeneration.

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NEUROPROTECTIVE EFFECTS OF INHIBITION OF HIF-PROLYL HYDROXYLASE IN HYPOXIA IN VITRO

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Hypoxia is a widespread pathological process. Hypoxia leads to functional and structural changes in tissues and organs even with short exposure. The brain is the most sensitive organ for oxygen deficiency. Investigation of the mechanisms that regulate concentration of oxygen in the cell is of special interest for the development of new drugs for hypoxia-associated diseases therapy. Hypoxia-induced factor (HIF) plays an important role in the cell molecular response to oxygen deficiency. The concentration of HIF is controlled by HIF prolyl hydroxylases (PHD) in an oxygen-dependent manner. Pharmacological inhibition of PHD leads to stabilization of HIF and could have therapeutic effect in ischemic damage treatment. The aim of our work was to study the neuroprotective effect of PHD inhibition under hypoxia.

First, we examined the effect of PHD inhibitor on the viability of primary hippocampal cell cultures under normal conditions to identify possible toxic effects of the substance on neural cells. Cell viability analysis showed that the PHD inhibitor in concentrations from 0.5 to 20 μM does not change number of viable cells compared to intact cultures. Treatment with 30 μM PHD inhibitor led to a significant decrease in the viability of the cell cultures. At the second stage of our work, we evaluated the possible neuroprotective effect of the PHD inhibitor in the acute hypoxic state model. Analysis of cell viability on the 7^{th} day of the posthypoxic period showed that preventive inhibition of PHD in concentrations from 0.5 to 20 μM leads to a significant increase of the cell viability of cell cultures versus “Hypoxia”. The ischemic diseases therapy is limited to the period of the “therapeutic window”. So, the next, we evaluated the possible neuroprotective effect of the PHD (1 and 15 μM) inhibitor upon application 2 hours after modeling hypoxia and further daily. It was shown, that PHD inhibition maintains the number of viable cells in culture (“Hypoxia” 73.11 ± 1.76%, “PHD 1 μm” 80.85 ± 1.41%, “PHD 15 μm” 80.70 ± 1.19%).

Our experiments revealed that PHD inhibition maintains viability of primary hippocampal cultures both during hypoxia modeling and in the posthypoxic period.

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MODULATION OF THE AMPLITUDE OF GAMMA-BAND OSCILLATIONS BY STIMULUS PHASE IN MOUSE VISUAL CORTEX NEURONS IMPROVES SIGNAL ENCODING

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Gamma band oscillations (25 - 70 Hz) play an important role in processing of information by neocortical neurons. In simple cells of the cat's visual cortex, it was previously shown that strength of gamma oscillations is modulated by the membrane potential oscillations at the temporal frequency of the stimulus, so that the gamma-band fluctuations are stronger at depolarization peaks, but weaker in hyperpolarizing phases of the stimulus frequency oscillation. More recently, theoretical studies using a conductance-based neuronal model have shown that this coupling significantly improves visual stimulus encoding. Due to the availability of a broad range of genetic tools, mice had recently become an important experimental subject for research in various fields of neuroscience, including visual physiology. It has been suggested that gamma oscillations in the mouse visual cortex play a minor role in visual processing due to the lack of specialized neurons that take part in generating gamma oscillations. Here we show, using patch clamp recording from simple cells in the visual cortex of anesthetized mice, that the strength of gamma oscillations is modulated by the phase of stimulus-induced oscillations during visual stimulation with moving gratings. In addition, using patch clamp recording from mouse visual cortex neurons in slices, we demonstrated benefits of gamma activity modulation for encoding of slow sinusoidal signals into sequences of action potentials. Thus, the phenomenon of amplitude modulation of gamma oscillations by temporal frequency of stimulus, originally described in the visual system of cats, may represent a universal mechanism that improves encoding of visual information which is present even in animals with a relatively poorly developed visual system, such as mice.

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CRISPR/CAS9-MEDIATED GENE EDITING AS A TOOL FOR MODELING AND TREATING NEURODEGENERATIVE DISEASES: ALZHEIMER'S DISEASE AS AN EXAMPLE

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Neurodegenerative diseases are a group of fatal, severe diseases characterized by primary pathology of CNS neurons. Among them, Alzheimer's disease (AD) is the most common age-related form of dementia. Despite extensive efforts, the understanding of the AD pathogenesis continues to be elusive. The pathogenesis of several familial forms of AD is relatively well studied. Mutations in the genes encoding presenilins *PSEN1* and *PSEN2* and the amyloid-β precursor protein (*APP*) are associated with early-onset AD whereas mutation in the gene encoding apolipoprotein E ε4 (*APOE ε4*) is associated with late-onset AD. However, genetic factors are responsible for no more than 10% of all early-onset AD cases, and only up to 25% of all late-onset AD cases are associated with the presence of the *APOE ε4* mutant allele [1]. Furthermore, genome-wide association studies have demonstrated possible associations between AD and mutations in more than 25 other genes.

CRISPR/Cas9 genome editing system provided a qualitative leap in the understanding of pathogenetic mechanisms and new approaches to therapy of AD. CRISPR/Cas9 can be applied in several areas of AD research. First, it can be used to discover new genes or mutations in the genes associated with AD pathogenesis. Second, CRISPR/Cas9 is used for AD modeling by introducing specific mutations into the genes to understand the consequences of newly found gene modifications. Third, modeling of specific aspects of AD pathogenesis. Finally, CRISPR/Cas9 is used for correction of known gene mutations in order to protect neurons and brain from degenerative alterations.

Dementia in AD starts from the impairments in short-term memory, which is probably related to functional alterations in the cholinergic system. Only a few data indicate the presence of polymorphism in the *CHAT* gene, encoding the central enzyme of acetylcholine metabolism choline acetyltransferase (ChAT) [2]. However, it is difficult to manipulate with *Chat* gene in rodents using the traditional methods. CRISPR/Cas9 allows to create knock-down of this gene in the adult brain. We develop a CRISPR/Cas9-based system which will allow to create *Chat* gene knock-down in the brain of adult mice. Seven single guide (sg) RNAs were selected in order to make a 41-nucleotide deletion in the encoding region of the *Chat* gene. Application of these vectors into 3T3NIH mouse fibroblasts was followed by successful expression of the constructs with 2.66% efficacy and the presence of mutations in the *Chat* gene was revealed using the T7 nuclease method. Several rLV- and rAAV-based vectors were prepared for the functional studies. Viral or plasmid vectors were used for transfection of NB41A of Neuro2a mouse neuroblastoma cell lines as a model of cholinergic neurons. Application of the vectors to neuroblastoma cells resulted in a decrease in the expression of ChAT protein detected using the Western blot method. Thus, CRISPR/Cas9 based gene editing may be used as a tool for ChAT gene knock-down in neuronal cultures and probably mature brain, but additional experiments should be performed to evaluate this opportunity.

Acknowledgements

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THE EFFECTS OF TRAUMATIC EXPERIENCE ON THE BEHAVIOR, C-FOS EXPRESSION AND FUNCTIONAL CONNECTIONS IN THE MOUSE BRAIN RESTING STATE NETWORKS

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Aims

It is known that the brains of animals and humans is active at resting state. In this paper we investigate how past experience affects characteristics of such resting state networks in animals. To do this we subjected mice to single traumatic experience that induced posttraumatic stress disorder (PTSD) and then analyzed activity of their brain (including cortex; hippocampus; amygdala; basal ganglia; thalamus; hypothalamus and midbrain) by c-Fos cellular mapping during traumatic memory retrieval and at rest in comparison with non-stressed animals.

Methods and Results

PTSD development led to global changes in brain activity: number of c-Fos-active neurons was significantly increased in different brain areas during traumatic memory retrieval. Similarly, PTSD induction strongly affects brain activity detected in resting state 7 days after: mice with prior traumatic experience had significantly increased number of c-Fos positive cells in comparison to naïve mice in cingulate cortex, retrosplenial cortex, parietal associative cortex, entorhinal cortex, basolateral and lateral amygdala, paraventricular thalamic nucleus and periaqueductal gray. Earlier these areas were shown to be involved in stress response and fear networks in humans and animals.

Using correlational analysis and graph theory approach, we revealed structure connectivity in resting state networks of naïve and PTSD mice, developed functional resting state networks and determined their main clusters. In both groups of mice clusterization exceeded random level. At the same time, these clusters did not interact well with each other: global efficiency of experimental networks was at the level of random network. Resting state networks of PTSD and control mice differed (Fig. 1): PTSD network was less clustered and longer paths linked the clusters. Induction of PTSD led to global changes in the structure of resting state networks. In naive animals, cortical regions had the most connections, whereas in PTSD thalamus, striatum and amygdala had. PTSD destroyed virtually all functional connections present in naive mice; only fully connected cluster of auditory and visual cortices remained. In addition, if in naive animals the main hubs were cingulate and retrosplenial cortices in PTSD animals paraventricular thalamic nucleus became the hub. In contrast, amygdala functional connectivity was virtually zero in naive animals, whereas in PTSD significant number of connections between amygdala, associative cortices, and striatum were observed.

In addition, we have shown that PTSD induction changes spontaneous behavior, causing elevated anxiety and decreased research activity in safe conditions of home cages. Behavior in conditioned fear, EPM and sensitization tests also changed, and these changes could be disrupted by protein synthesis inhibition during traumatic experience, which also returned brain activity and structure of resting networks to normal in PTSD animals.

Conclusions

Our findings show that stressful experiences can alter spontaneous behavior, induced and spontaneous brain activity and patterns of functional connections in resting state neuronal networks long after traumatic episode. We assume that these changes reflect replay of neuronal ensembles of the animal's past subjective experience. This assumption was tested by disrupting the development of PTSD.

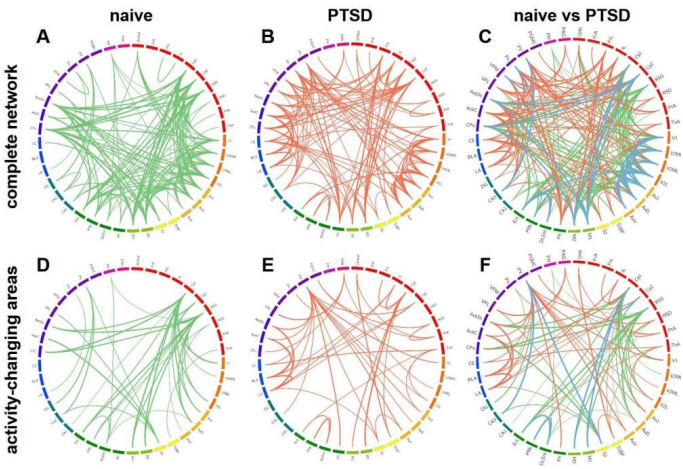

Fig.1. Resting state networks of naive mice (A, D) and PTSD animals (B, E), and their interception (C, F). A, B and C are for complete resting state networks, and D, E and A represents only connections of 11 brain areas that significantly change their activity in PTSD compared to naïve mice. Lines are Pearson's correlations with $R>0.5$, $p<0.05$; green lines – naive resting state network; red lines – PTSD resting state network; blue lines – correlations that are present in naive and PTSD mice

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SEROTONIN INDUCES AN INCREASE OF NUCLEAR CALCIUM LEVELS IN CORTICAL NEURONS EXPRESSING GCaMP6f

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It is known that serotonin can regulate calcium release, which can impact various intracellular processes, from activation of protein kinases to triggering gene expression. Increasing evidence indicates that nuclear calcium signaling of neurons is the link between the activity of neurons and transcription-dependent synaptic changes that determine the plastic properties of the nervous system. Therefore, a thorough analysis of the interaction of these mechanisms and understanding of how serotonin affects nuclear calcium signaling was a crucial aim of this study.

C57Bl6 males (P40-50) were used as an object. We used a genetically-encoded nuclear-targeted Ca^{2+} indicator GCaMP6f, allowing reporting of nuclear calcium signals. AAV2_pSyn_H2B-GCaMP6f was injected into the mice, the construct was based on the adeno-associated virus of the 2nd serotype (https://www.addgene.org/102994/) and the sequence of the calcium sensor protein GCaMP6f (https: // www.ncbi.nlm.nih.gov/pmc/articles/PMC3777791/) under the neuron-specific synapsin promoter. GCaMP6f was linked with histone H2B, which ensured its localization in the nucleus. Two weeks later mice were deeply anesthetized with isoflurane and decapitated for the slices preparation. Brains were rapidly removed and placed in ice-cold artificial cerebrospinal fluid (ACSF). Brain slices (300 μm) were cut using a vibratome (VT1200 S, Leica). The slices were incubated at room temperature at least for 60 min. Live-cell imaging was performed with an LSM 5 LIVE DuoScan confocal microscope (Zeiss) equipped with a chromatically corrected water immersion lens (Plan Apochromat IR DIC 63×, 1.0 NA, Zeiss). We imaged L5/L6 pyramidal neurons in the line scan mode (equivalent to imaging with a linear charge-coupled device) using a 488-nm laser and 505 long-pass (LP) emission filter. The measured optical signal reflected the change in fluorescence relative to its mean value ($\Delta F/F$). The recorded neurons were located at a depth of 30 to 40 μm from the slice surface.

We performed three types of experiments. In the first one we imaged nuclear calcium dynamics in mice slices in response to serotonin ($2x10^{-5}$ M). The next step was to investigate the mechanisms by which serotonin induces Ca^{2+} signaling in the nucleus. We carried out a pharmacological manipulation with intracellular Ca^{2+} store and release mechanisms – we used caffeine, a potent agonist of the RyR receptors that increases its sensitivity such that resting cytosolic Ca^{2+} levels may become stimulatory, and dantrolene, which inactivates the RyR receptors. In experiments in which cells were treated with dantrolene (50 μM final concentration) the cells were first incubated in 50 μM dantrolene for 20 minutes prior to the start of imaging, then serotonin was applied. Cortical pyramidal neurons preincubated with caffeine (10 mM final concentration) for 5 minutes were then treated with serotonin.

In our first type of experiments we measured calcium responses in nuclear compartment to the serotonin application. We observed two types of serotonin-mediated events. 1. Serotonin application to cortical neurons elicited Ca^{2+} elevation in nucleus (n=18) (up responses). 2. Serotonin application to cortical neurons elicited Ca^{2+} decrease in nucleus (n=11) (down responses). To quantify these effects, we measured the fractional change ($\Delta F/F$). The mean $\Delta F/F$ measured for up responses was 29.0 ± 5.4% and 9.6 ± 1.1% for down responses. Statistical comparison of the two showed that they were significantly different ($p<0.05$).

In the second type of experiments, preincubation of cortical pyramidal neurons (n=6) with caffeine (and thus sensitization of RyR receptors) and subsequent serotonin application led to a decrease of the Ca^{2+} response amplitude. Bath applications of caffeine induced Ca^{2+} elevations in nuclei. The mean $\Delta F/F$ was 12.9 ± 9.3%. Serotonin applied for 5 minutes after caffeine administration also elicited a significant Ca^{2+} increase in nuclei (11.7 ± 3.2%). However, the serotonin-mediated Ca^{2+} signal after caffeine was significantly less than serotonin-

mediated Ca^{2+} signal only ($p<0.05$). These results indicate that an increase in nuclear Ca^{2+} elicited by serotonin depends on Ca^{2+} release from intracellular stores.

In the third part of experiments we found that application of dantrolene partially inhibited the amplitude of serotonin-induced increase in nuclear Ca^{2+} signal. The mean $\Delta F/F$ was 9.4 ± 1.1% (n=12) and that was significantly less than the serotonin-mediated Ca^{2+} signal only ($p<0.05$). Moreover, we observed that dantrolene changed the shape and kinetics of nuclear calcium signals. Ca^{2+} elevations in dantrolene-treated cells achieved its peak amplitude faster than in control cells (only serotonin administration). After reaching the peak amplitude, a rapid extinction of the calcium signal was observed. Thus, calcium elevation mediated by serotonin without dantrolene was bigger in amplitude, slower to reach their peak concentration, lasted longer and decayed more slowly. To confirm the efficacy of dantrolene, we applied caffeine after the incubation with dantrolene. Caffeine-induced Ca^{2+} elevations were prevented by the inactivation of RyR receptors with dantrolene. These data indicate that increase in nuclear Ca^{2+} caused by serotonin represents a dantrolene-sensitive Ca^{2+} release from intracellular stores.

We concluded that serotonin can cause two distinct forms of nuclear Ca^{2+} responses, increase and decrease. It should be noted that state- and cell type-dependent difference may contribute to observed diversity of experimental evidence. Serotonin-mediated nuclear Ca^{2+} signal in cortical L5/L6 neurons was reduced in amplitude in the presence of dantrolene and after the induction of the RyR-mediated Ca^{2+} signal with caffeine. The results obtained demonstrate that an increase in nuclear Ca^{2+} elicited by serotonin seems to be dependent of RyR receptors contribution, and nuclear elevations were dependent at least partly on the perinuclear calcium release. Another possible mechanism that can contribute to nuclear calcium events after serotonin administration is a diffusion of cytosolic calcium through nuclear pores. All in all, the mechanisms of serotonin-mediated nuclear calcium events are an intensively investigated topic that could involve different paths, and this topic requires further investigation.

Acknowledgements

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BIOPHOTONICS

Biophotonics is a wide-range scientific discipline that studies the phenomena and methods associated with the interaction of biological objects and photons and using different light sources to obtain information about the condition of biological objects in normal and pathological states

This section accepts abstracts on the following topics and issues:

- Biophotonics in basic research and clinical applications
- Biophotonics in cancer and stem cells research
- Optical bioimaging of animal and plant cells
- Nanophotonics
- Optogenetics
- Agrophotonics
- Development of laser-spectroscopic methods for biological molecules studies
- Optical methods in food and processing industry
- Mathematical modeling the processes of interaction between electromagnetic radiation and matter
- Modern devices and software for biophotonics

NANOPARTICLES OF DONOR-ACCEPTOR MOLECULES AS LIGHT-CONTROLLED STIMULATORS OF NEURONAL ACTIVITY

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Organic semiconductors are in general biocompatible and prospective materials for various biological applications, such as visualization and elimination of tumors, and, recently for photostimulation of excitable cells. Moreover, some organic conjugated materials have both ionic and electronic conductance, opening possibility to design a bio-electronic interface. Among the organic semiconductors one of the most promising class is donor-acceptor (D-A) molecules. Varying of donor and acceptor fragments one can tune absorption and luminescence spectra and energy levels of the molecules [1]. This allows researchers to control the live systems precisely via light of certain wavelengths.

Here we present pilot results of experiments on the nanoparticles made of organic conjugated molecules. First, using confocal microscopy we show that the nanoparticles were not internalized by neurons of rat primary cortex culture. Then, using patch-clamp technique on rat primary culture we demonstrated light-controlled electrical responses of neurons. We show that magnitudes of the responses are wavelength-dependent, according to the nanoparticles absorption spectrum. Varying chemical structure of the D-A molecules, we were able to show dependency of the responses magnitude on the size of side alkyl chains of the molecule, suggesting its lipophilic properties are important to design a bio-electronic interface.

Acknowledgements
The work was supported by the Russian Science Foundation (grant 19-73-30028).

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CYTOCOMPATIBILITY AND ANTIBACTERIAL PROPERTIES OF A COATING BASED ON SYNTHESIZED NANOSTRUCTURED CARBON

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The development of a coating with a pronounced antibacterial activity against a wide range of microorganisms in combination with good biocompatibility is one of the priority directions for modern nanotechnology.

Our team has developed an electrospark technology for producing a colloidal solution containing nano-sized amorphous carbon. The advantages of this technology are low cost and high performance. The colloidal solution of the obtained nano-carbon has a very high stability. Coatings based on it are nanostructured. They are highly adhesive and hydrophobic.

The antibacterial and cytotoxic properties of this coating have been investigated. The obtained nanocarbon coating was shown to have bacteriostatic properties against gram-negative *Escherichia coli* and gram-positive *Staphylococcus aureus*. A decrease of one order of magnitude in the growth rate of *E. coli* cells and an almost six-fold decrease in *S. aureus* was noted.

The study of the cytocompatibility of the coating was carried out using the SH-SY5Y cell line (human neuroblastoma) as an *in vitro* test system. A culture glass and a medical titanium nickelide alloy (Ni-Ti, nitinol) were used as controls.

According to the results of the assessment of cell viability, the number of non-viable cells grown on the culture glass did not exceed 3%, while the number of non-viable cells in the cultures growing on nitinol and nanocarbon coating was 5% and 7%, respectively. It should be noted that the data on the viability of cells grown on medical alloy and nanosized carbon coating did not differ statistically. However, when nitinol or nanosized carbon coatings are used as a substrate, the number of non-viable cells is almost doubled relative to culture glass. It was found that the mitotic index of cells growing on the surface of the nanocarbon coating corresponds to the mitotic index of cells growing on a medical alloy of nitinol. For the SH-SY5Y culture, the mitotic index is about 2.5%. When using nitinol plates or nanosized carbon coating as a substrate, the mitotic index is about 1.5%. Thus, the mitotic index of cell cultures growing on the surface of a nanosized carbon coating corresponds to the mitotic index of cells growing on medical nitinol. It was found that for 72 h on all investigated surfaces (culture glass, nitinol, nanosized carbon coating), the cells did not form a continuous monolayer, although in some parts of the culture there were monolayer elements. On the surface of the culture glass, cells occupy about 80% of the surface available for growth. On the nitinol surface and nanoscale carbon coating, cells occupy about half of the available area. The density of cell cultures growing on a nano-carbon coating did not statistically differ from cultures growing on culture glass or nitinol medical alloy.

Thus, the obtained nanostructured carbon coating possesses bacteriostatic properties, but does not have a significant toxic effect on SH-SY5Y cells. We assume that the coating developed by our team, it may be interesting for applications in medicine and food industry for the long-term antibacterial surface treatment.

MULTIPARAMETRIC OPTIMIZATION OF THE CAROTENOID LINEAR OPTICAL RESPONSE SIMULATION

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A task to simulate the linear optical response in pigment molecules, e.g. carotenoids, requires the solution of several problems related to optimization [1]. One of the biggest problem that one has to choose between the quality of the results and the calculation time. Another problem is that with the growing of the number of free parameters, the probability of finding the right solution decreases because the algorithm sticks at local minimum. To overcome these problems, we will use Differential Evolution (DE) algorithm [2], which fits the experimental data by iteratively improving a candidate solution imitating evolutionary processes. To simulate absorption spectra and to find the optimal parameters of the model, we have to find the best strategy type of the algorithm for our optimization problem.

To control convergence of the fitting procedure, DE allows choosing one of 10 strategies DE/x/y/z and two adjusting parameters *F* and *Cr*. The choosing strategy of DE creates mutant vectors and then employing the crossover operation. Finally, we get a new generation of model parameters and classify them according to the best fitness with experimental data.

To check the rate of DE convergence, we do not apply the measured absorption spectra as the target function, but use the simulated one. We did it because the simulated spectra provide us the perfect fit after finish of the optimization procedure. The multimode Brownian oscillator model [3, 4] was applied to get the shape of the simulated spectrum roughly corresponding to that of carotenoid absorption in solvents.

Both parameters *F* and *Cr* are varied in the interval from 0.1 to 1.0 with discrete step 0.1. Thus, the total number of DE/x/y/z;Fk1,Crk2 combinations equals 1000. The best solution averaged over 5 DE runs was obtained for strategy DE/best/1/bin and reached 16th order of magnitude. Spectra simulations were performed by using software that includes the algorithm of DE and procedures of linear optical response modelling. The block scheme of multiparametric optimization of the carotenoid linear optical response simulations shown on Figure 1.

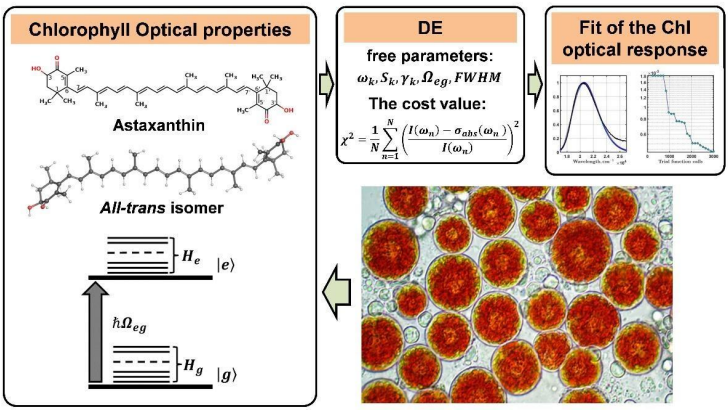

Fig. 1. The block scheme of multiparametric optimization of the carotenoid linear optical response simulations

As the result, we estimated *F* and *Cr* parameters to reach maximum performance of DE and then we fitted real experimental data with reasonable accuracy. Performing this fit, we got a set of the multimode Browning oscillator model parameters. Several of them were determined with high precision, however for some of them the standard deviation was large enough to consider them well defined. This is due to the lack of additional

experimental data, for instance, Raman spectra of carotenoids. Thus, we suppose that by applying the DE algorithm to model absorption we have obtained some parameters characterizing the electron-phonon interactions.

Acknowledgements

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DEVELOPMENT AND APPLICATION OF PHOTOCONVERSION FLUOROPOLYMER FILMS FOR GREENHOUSES

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To convert and store energy in the process of photosynthesis, plants primarily use quanta of the red and blue parts of the spectrum. At high latitudes, the average daily intensity of red and blue parts of the spectrum is not very high; for many crops cultivated under greenhouse conditions, it reaches the sufficient level only on clear summer days. The problem of insufficient illumination in greenhouses is usually solved with artificial light sources. We offer a solution to the problem of low light with photoconversion films. This short communication describes a technology for the manufacture of photoconversion fluoropolymer films for greenhouses (Fig. 1).

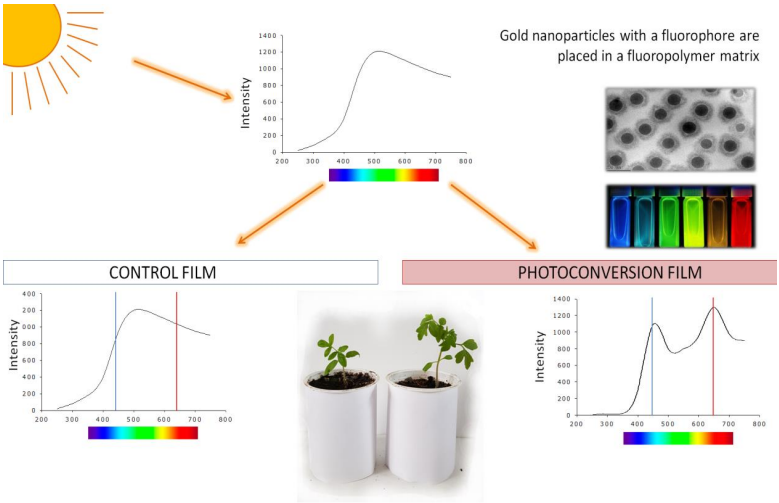

Fig.1. The concept of the presented work. The upper graph shows the energy spectrum of the sun on the surface of the Earth. When passing through the control film, it does not significantly change (lower left graph). When passing through fluoropolymer photoconversion films, its contribution to the blue and red components increases (lower right graph). As a result, in high latitude conditions, plants growing under a fluoropolymer photoconversion films have an advantage

In the course of work, using laser ablation, gold nanoparticles were obtained and investigated. The production of quantum dots was carried out, the main physicochemical parameters of these quantum dots were investigated. A technology for low-temperature implantation of quantum dots and gold nanoparticles into polymers has been developed. To assess the efficiency of photoconversion films, morphometric studies of plants cultivated under control conditions and under various photoconversion films were carried out. The photosynthetic activity of plants, the rate of transpiration, and the system of signaling electrogenesis were studied.

The fluoropolymer films described in the paper make use of original gold nanoparticles and original nanoparticles with fluorescence in the blue or red region of the spectrum. In the polymer film, nanoparticles aggregate in the form of “beads”, which enhances the field of the optical wave. The film photoconverts UV and violet light into blue and red light. Gold nanoparticles also partially convert energy in the green region of the spectrum (not used by plants) into heat, which is also important for agriculture at high latitudes. In addition, impregnation of gold nanoparticles into fluoropolymer significantly increases the lifetime of the film.

The films described in the paper can significantly increase the productivity of greenhouses [1-3]. Plants cultivated under the films have more chlorophyll and a higher intensity of photosynthesis – although their system of distance stress signals is, to a certain degree, suppressed.

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LASER SPECTROSCOPY FOR IN-SITU CHEMICAL ANALYSIS DURING METAL ADDITIVE MANUFACTURING

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Remote laser sensing provided unique capability to quantitatively analyze any target which can be reached by photons. Specifically, Raman spectroscopy and laser induced breakdown spectroscopy (LIBS) techniques are powerful tools for molecular and elemental analysis respectively including *in situ* and real time analysis for both organic and inorganic samples. A new generation technology, metal parts production by additive manufacturing, opens new powerful capabilities including direct synthesis from three-dimensional digital models as well as superior flexibility for producing internal structures which cannot be fabricated by traditional machinery and unique possibility to grow parts with required design of chemical composition gradient. The improvement of online control systems is essential for high quality production as well as advancement of additive manufacturing into high-value applications where component failure cannot be tolerated.

For the first time, we have demonstrated the feasibility of in-situ quantitative elemental analysis by LIBS during metal samples production by additive manufacturing [1,2]. We developed a low weight and compact remote LIBS system which quantitatively analyze both light and heavy elements during composite coating (nickel alloy reinforced with tungsten carbide particles) synthesis by co-axial laser cladding technique. Coaxial laser cladding is an additive manufacturing technique based on metal powder flow melting by powerful continuous wave laser.

Owing to non- uniform distribution of tungsten carbide grains in the upper surface layer the only acceptable choice for LIBS analysis was in the melt pool at a growing clad. Luckily, we have not detect any impact of LIBS sampling on lad properties. The feasibility of in situ LIBS quantitative elemental analysis of key components (carbon, tungsten and nickel) has been demonstrated during the cladding process. In situ LIBS analysis was in a good agreement with the offline measurements by X-ray fluorescence spectroscopy (XRF) and combustion infrared absorption method (CIAM). Finally, LIBS technique was demonstrated to be a good tool for real-time detection of cladding process.

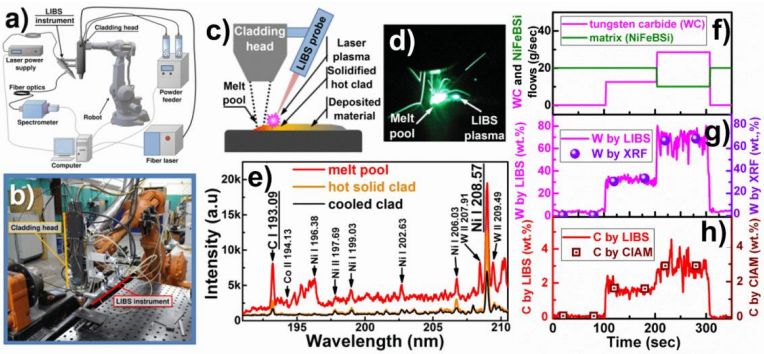

Fig.1. Scheme (a) and photo (b) of the coaxial laser cladding setup equipped with the laser induced breakdown spectroscopy (LIBS) system. LIBS sampling spots (c), plasma photo (d) and plasma spectra (e). WC

and NiFeBSi powders flows for gradient coating (f). In situ LIBS analysis for W (g) and C (h). W and C were verified by X-ray fluorescence spectroscopy (XRF) and the combustion infrared absorption method (CIAM).

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DESIGNING THE QUANTUM MODELS OF ENERGY MIGRATION AND ELECTRON TRANSPORT IN PHOTOSYNTHETIC PIGMENT-PROTEIN COMPLEXES

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Phenomenon of photosynthesis is a specific combination of physical and chemical processes occurring in .higher plants, bacteria, and algae that are driven by the incident light coming from the Sun. Light quanta of the visible range being absorbed by the pigment-protein complexes of photosynthetic species, through the sequence of acts of energy migration and redox reactions, is converted to the chemical energy, which is stored by a living organism in the form of carbohydrate molecules [1].

The characteristic rates of photosynthetic processes are rather wide: form femtoseconds that scale the processes of energy conversion and exciton migration in the light-harvesting complexes, to milliseconds describing the chemical reactions. The ultra-fast physical processes of photosynthesis (10^{-15}s-10^{-12}s) usually include the acts of energy absorption, exciton formation and further energy migration to the so-called reaction centers where charge separation takes place [2].

The standard experimental techniques to investigate the energy migration in the pigment-protein complexes (often they are called light harvesting complexes) isolated from photosynthetic organisms are those of the linear and nonlinear optical spectroscopy. By measuring and modeling the linear and nonlinear optical responses we can unveil physical mechanisms which control the energy transport and charge separation in these complexes.

Pigment-protein complexes are the essential parts of photosynthetic machinery. Without going into details, we can say that they consist of a protein matrix and pigment molecules: chlorophylls, (or bacteriochlorophyls) and carotenoids. The protein matrix works as a skeleton for the pigments; it rigidly fixes their location in antenna thus forming a spatial configuration of interacting molecules. The number of pigments in such complexes could be form tens to thousands [1]. Since the spatial arrangement of pigments in antenna complexes is not strictly symmetric, the application of mathematical methods (group theory, for example) does not allow simplifying the problem and obtaining an analytical solution. Moreover, the situation is complicated by the presence of different protein environment around pigment molecules, which strongly affects the optical properties of individual pigments in the antenna. Thus, in order to evaluate the optical response of a photosynthetic antenna, it is necessary to operate with large volumes of heterogeneous information, as well as to solve integro-differential equations for virtually every pigment molecule in the antenna.

To model the experimental data of optical measurements taken on samples of photosynthetic antenna complexes, it is necessary to solve a quantum problem of a system for which the external electromagnetic field is considered as a perturbation [3]. In this case, the system can be quantized (i.e., the eigenvalue problem is solved for it) invoking the semiclassical approximation. With this approach, we can simultaneously simulate the results of different spectroscopic measurements on the same sample, thereby increasing the chances of finding system parameters that can be used to predict the optical response for different experimental designs [4].

It is obvious that the solution of such complex problem is possible only when modern computational facilities allowing operating with a large amount of the data characterizing both individual molecules, and groups of molecules. The key point is to optimize the procedure for calculating the relaxation tensor (calculated according to the theory of Redfield), characterizing the rate of redistribution of excitation energy in the antenna. A special software, which contains both procedures for calculating the physical properties of the pigment and

procedures that control the distribution of data of the simulated system, as well as the implementation of a parallelized optimization algorithm for modeling experimental data, has been successfully developing by our research group for the last ten years [5-6].

Acknowledgements

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LASER INTERFEROMETRY AND OTHER OPTICAL METHODS FOR STUDYING LYSOZYME DENATURATION

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The processes of protein denaturation in hen egg white lysozyme (HEWL) were studied using various optical methods (laser interferometry, UV/visible absorption spectroscopy, dynamic light scattering). All measurements were carried out in a cuvette directly during the reactions of denaturation. The solvents (50 mM Tris-HCl, pH 8.0) were selected so that protein denaturation occurs either without aggregation or with aggregation. In the first case, 6M guanidine hydrochloride (GdnHCl) and 30 mM dithiothreitol (DTT) were added to the solution with the protein, in the second case were added DTT only. The enzymatic activity of HEWL was measured by using the lyses of *M. lysodeikticus* cells as a control for the native state of the protein.

We found out that HEWL almost completely loses its enzymatic activity after 30 minutes and its hydrodynamic radius increases from 3.8 nm to 5.7 nm at the same time. On the contrary in the reaction with only DTT protein remains approximately 40% of its enzymatic activity after one hour. In this case, protein aggregates tens of nanometers in size are formed in the first minutes after the start of the reaction. Aggregates reach micron sizes after an hour in denaturing solution.

It was shown that the lineshape of the spectra obtained by absorption spectroscopy was changed in the UV range in denaturation reaction with GdnHCl and DTT and in the visible range for denaturation with only DTT. However, in the case of solutions with 6M GdnHCl, spectroscopic measurements are difficult due to the high absorption in the UV region (λ <280 nm).

Another way to study the HEWL denaturation is the laser interferometry. Earlier it was shown that the refractive index of protein solutions increases in the reaction of protein hydrolysis by pepsin [1]. An increase in the refractive index by ~ $4.5 \cdot 10^{-5}$ was also found in the denaturation reaction with GddHCl and DTT. More details can be found in [2,3].

Relationships have been established between the measured parameters of protein solutions, investigated by interferometry, DLS, and spectroscopy. The previously developed model [1] shows that interferometry gives

information about the hydration shell around protein molecule but not about the structure of protein. As a result, it is clear that interferometry does not compete with methods presented in the work and other methods for studying protein structure, as well as spectrofluorimetry, circular dichroism, etc. Interferometry provides new information on the nature of the interaction of a protein with a solvent.

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PHOTODYNAMIC THERAPY LAUNCHES IMUNOGENIC CELL DEATH OF BRAIN GLIOMA CELLS

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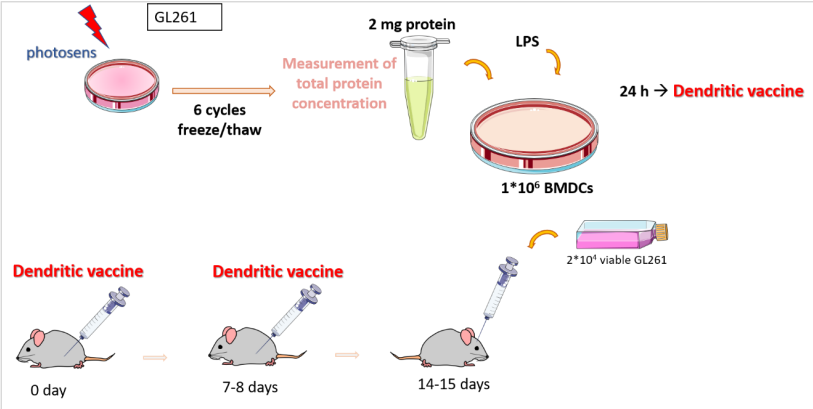
Limitations of anticancer therapy are specificity to tissue type, tumor location, cytotoxic effect on healthy organs. Therefore, therapy is more successful when it can induce an immunogenic form of cancer cell death (ICD). ICD is characterized by the emission of danger molecules (DAMPs), leading to the induction of strong anti-tumor immune responses. It has been shown the high efficacy of photodynamic therapy (PDT) in the treatment of tumors. In our research we want to show, that some photodynamic agents can induce ICD and trigger anti-tumor defense in vitro and in vivo.

We choose a photosensitizer, that used in clinical protocols – photosens (Niopik, Russia) (ссылка на его создателя). The efficacy of photosens (PS) has already been shown in vitro in the MCA205 line, and a vaccine based on photosens-PDT-induced cells protected mice from tumor development in a syngeneic model (Turubanova et al., 2019). First, we identified the optimal concentrations of photosensitizers and found that in the doses of 20 J/cm2 they efficiently induce cell death in the murine glioma (GL261) cell line. Intracellular distribution of PS was studied by using the laser scanning microscope. Tumor cells undergoing PS-PDT induced cell death emit calreticulin, HMGB1 and ATP and they were efficiently engulfed by bone-marrow derived dendritic cells, which then matured, became activated and produced IL-6.

Using dying cancer cells induced by photosens-PDT, we demonstrate the efficient vaccination potential of ICD in vivo. In the model, activated dendritic cells have become a powerful stimulus for the activation of T-cell populations.



We assessed the survival rate of animals, visualized the tumor focus in the brain by magnetic resonance imaging, assessed the size of developing tumors, analyzed the neurological status of the animals during the experiment.

As a result of the use of a dendritic vaccine based on photoinduced cells that die by the immunogenic pathway, it has been shown that the survival rate of mice is significantly higher than that of unvaccinated mice. From 15 to 18 days after inoculation of cells into the brain, all mice of the control group died. The dendritic cell vaccine based on PDT-photosens of glioma cells resulted in a significant survival rate of animals in the experiment, less manifestation of symptoms of neurological deficit and caused the development of a smaller tumor in comparison with the control groups.

Thus, this indicates the immunogenicity of the death of tumor cells after photodynamic exposure and is the basis for a therapeutic protocol for the using of a dendritic vaccine.

Acknowledgements

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PARAMETERS OF PHOTOSYNTHESIS AND PRODUCTIVITY OF LETTUCE DURING GROWTH UNDER LIGHT WITH DIFFERENT SPECTRA

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Currently, agricultural technologies are aimed at increasing the productivity of plants and their tolerance to stressors. Search and maintenance of optimal plant illumination regimes is one of the key tasks for growing plants in greenhouses in modern agriculture. Sunlight or mixed light (sunlight + artificial light) are mainly used in greenhauses, however, the transition to fully artificial lighting and supplementary lighting for year-round production creates the potential for optimizing plant growth and development. The aim of this work was to assess the effect of growing lettuce plants under different light spectra on photosynthesis and productivity.

Lactuca sativa L. “Azart” were grown hydroponically on mineral wool cubes using a Flora Series® fertilizer complex. The illumination was carried out by phyto-irradiation system composed of LED lamps with

different ratios of three spectral channels: blue, red and white. HPS lamps were used in control lighting. The content of photosynthetic pigments was assessed using a portable chlorophyllometer CL-01. Photosynthetic studies were carried out using the PAM-imaging system an Open FluorCam FC 800-O/1010. Registration of gas exchange parameters was carried out using GFS-3000. Primary productivities of plants were assessed by the wet and dry weight.

It was shown that growing under control conditions led to the least increase in total biomass and dry weight, which indicates low plant productivity under these conditions. In contrast, the use of combined lighting with white, red and blue LEDs increased the productivity of the plants. The highest productivity was observed with using a combination of high intensity of red and low intensity of blue light.

Content of photosynthetic pigments and quantum yield of photochemical reactions in plants grown at high intensity red and low intensity blue light did not differ significantly from other LED lighting. However, the analysis of electron fluxes showed that plants grown under conditions of high intensity of red light have a large amount of photosynthetic electron flux.

Acknowledgements

The investigation was funded by the Ministry of Science and Higher Education of the Russian Federation for large scientific projects in priority areas of scientific and technological development, contract no. 075-15-2020-774.

NEURODYNAMICS AND ARTIFICIAL INTELLIGENCE

The topic of the section "NEURODYNAMICS AND ARTIFICIAL INTELLIGENCE" relates to the study of neural oscillations and various dynamic modes of communication of neurons, neuronal ensembles and systems in relation to the development of theories and applications of artificial intelligence.

Section topics include, but are not limited to:

- Artificial neural networks
- Machine learning for neuroscience
- Evolutionary computation for neuroscience
- Neuroinformatics
- Multi-scale analysis in neuroscience
- Intelligent Robotics
- AI based data processing methods
- Artificial intelligence in statistics

STATISTICAL ANALYSIS OF COUPLING EVOLUTION IN ABSENCE EPILEPSY MODELS FROM SIMULATED AND EXPERIMENTAL DATA

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The aim of this work is to distinguish differences between two approaches to statistical evaluation of coupling detection results. We analyze both real data obtained from WAG / Rij rats — genetic models of absence epilepsy [1] — at spike-wave discharges (SWDs) and simulated data from simple SWD model [2].

Methods

In this work, 130-minute 4-channel (frontal (FC), parietal (PC) and occipital cortex (OC) and hippocampus) recordings of intracranial EEG from 8 male WAG/Rij rats were analyzed, with K=28 for each animal in each experiment. All seizures were spontaneous. The length of the selected seizures was at least 6 s. Seven stages of 2 s length were extracted from each seizure. The analysis was performed for each stage:

1.background activity, [−5; −3] s before the seizure onset;
2.preictal activity, [−2; 0] s before the seizure onset;
3.decoupling, [0; 2] s after the seizure onset;
4.seizure maintenance, [2; 4] s after the seizure onset;
5.termination, [T-2; T] s before the seizure termination
6.posticta1 stage, [T; T+2] s after the seizure termination;
7.recovery activity, [T+2; T+4] s after the seizure termination.

The transfer entropy (TE) [3] — a popular nonparametric measure of directed connectivity was used to analyze the data. The efficient technique described in [4] was chosen for numerical calculation of TE because it has smallest requirements for the data amount. Two ways of statistical detection of changes from baseline coupling level (stage 1) were compared. The first one is traditional Student's t-test for mean values like in was

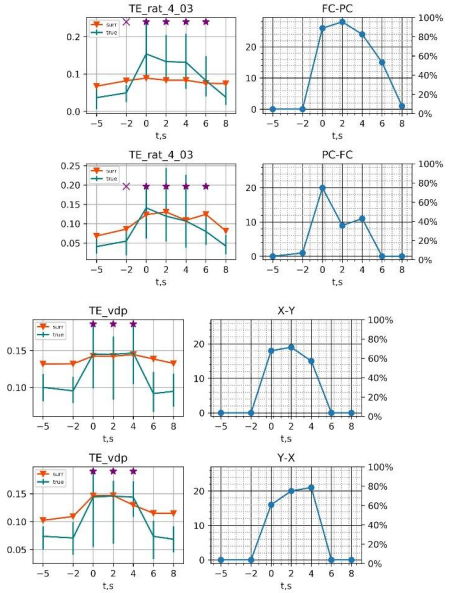
previously applied [5]. The second approach is based on surrogate testing and uses number of significant coupling findings as a measure of coupling strength rather than the raw TE values [6]. To test the results on significance, Ks=KK-1=756 surrogate time series were built by rearranging realizations (all possible combinations of all possible episodes for a pair of channels, except when they are from the same episode). This number of surrogates allows us to obtain a high confidence level of 99.87%, which is important because multiple testing. To provide etalon simulations and detect differences between approaches, we ensembles of parametrically coupled generalized van der Pol—Toda oscillators shown in [2] to be able to reproduce some SWD characteristics and test both approaches to statistical analysis.

$$X=(x1,x2,\ldots,xM)T, \quad 1)$$

where xn is a state of the system at time moment n.

Results

Results the transfer entropy for the channels FC and PC (rat #4) are shown in Fig. 1 a,b and for two bidirectionally coupled oscillators are shown in in Fig. 1 c,d. One can see that both approaches to statistical analysis show the large correspondence. For oscillators they indicate significant coupling TE increase from the baseline level (stage 1) in stages 3-5. For experimental data the t-test shows the preictal increase in both directions and postictal increase for PC→FC direction which is not indicated using the surrogate-based analysis.



(a) (b) (c) (d)

Fig. 1. Average (cyan line), minimal and maximal (cyan errorbars) values of transfer entropy (a, c) and the number (left Y-axis) and percentage (right Y-axis) of statistically significant results (b, d) for experimental data (a, b) and for ensemble of for oscillators (1) (c, d) plotted over starting point of considered time interval. Orange curve on plots (a, c) shows the maximal surrogate level and violet stars (p-value = 0.001) and crosses (p-value = 0.05) indicate the significant increase over baseline TE level (stage 1, -5 s).

Here we see that the surrogate analysis should be considered as more conservative way of statistical analysis of coupling detection results. However, results of two types of analysis match one another well, supporting the outcomes and conclusions of [5,7].

Acknowledgments

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RECOGNITION OF HANDWRITING FROM ELECTROMYOGRAPHY WITH DEEP LEARNING

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Handwriting is one of the most distinctive features of human culture that relies on cortical motor control of fine movements. Handwriting suffers in neural trauma and disease, and need to be restored in patients that lack this skill, such as amputees. To this end, we have developed a deep-learning approach for decoding handwriting patterns and font characters from electromyographic (EMG) signals recorded from eight muscles of the hand and forearm. Decoding with deep learning exceeded the previous results obtained with different methods. Thus, our findings demonstrate the practicality of generating handwriting based on EMG signals – the result that could be useful for controlling prosthetic hands and diagnosing neurological conditions. Our decoding methods are also applicable to the systems that measure muscle properties with alternative approaches.

ROTATIONAL DYNAMICS VERSUS SEQUENCE-LIKE RESPONSES

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In a recent review on neural population dynamics, Vyas et al. commented on our previous observations regarding the contribution of sequences-like responses to rotational dynamics patterns in the activity of cortical neuronal population revealed with a dynamical variant of principal component analysis (jPCA). According to Vyas et al., rotations generated from sequence-like responses are different from the ones present in empirical neuronal patterns, which are highly heterogeneous across motor conditions in terms of response shape and timing. In response to this claim, here we extend our previous findings with new results showing that empirical population data contain neuronal responses whose shape and timing persist across arm-movement conditions. The more complex, heterogeneous responses are also present in the empirical data. The heterogeneous patterns contain temporal sequences, which can be revealed with the analysis of the time course of cross-condition variance. Combined with simulation results, these observations show that both consistent and heterogeneous responses, organized in sequences, contribute to jPCA rotational patterns. We suggest that the users of jPCA should consider these two contributions when interpreting their results. Overall, we do not see any principal contradiction between the neural population dynamics framework and our results pertaining to sequence-like responses. Yet, questions remain regarding the conclusions that can be drawn from the analysis of low-dimensional representations of neuronal population data.

REAL-TIME NEUROSIMULATIONS

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In this paper, we will review the technologies that could be used for bio-plausible neurosimulations in real-time only software implementations. For historical reasons the neurosimulations field is formed with models based on Hodgkin–Huxley [1]. This model is based on calculation of membrane currents and could be easily expanded and constructed according to the requirements of the simulation including the receptors' kinetics, pharmacological agents diffusion, etc. The ModelDB [2] contains 345 models based on Hodgkin–Huxley (H-H) [1], 55 – Izhikevich [3, 4, 5] and only 5 – FitzHugh-Nagumo (FHN) [6]. The main disadvantage of the H-H model is computational cost that prevents it from being used in real-time simulations even using modern computers and clusters.

There are two popular models that were built on base of H-H for the computational effectiveness Izhikevich and FHN. The model of Izikevich [3, 4] is capable of several spiking modes and real-time simulations of 500,000 neurons and 50 million synapses [7], we have failed to find similar data for FHN though there are some works dedicated to performance of the FHN model [8, 9]. Recently we have introduced the even simpler real-time neuron model (ESRN) [10] where we presented the model using which we could implement the real-time calculation of neuronal activity of the basic generators Oscillator motifs of the spinal cord.

Neurosimulations are traditionally used for the bio-plausible implementation of biological phenomena. We proposed that close to biology neuromorphic models could be used for different purposes including neural interfaces, neuroprosthetics, neuromorphic processing for pattern recognition, and locomotion management in AI and robotic systems [12].

The outbound neural interfaces could exploit the real-time neurosimulations as neural pattern recognition mechanisms with STDP self adaptation, the inbound could make use of basic neuronal generators to produce the

neuronal “native” patterns for the nervous system stimulation. In the neuroprosthetics real-time models could play the role of missing/damaged part of the nervous system integrated via neural interface. As for robotics and AI the applications seem to make a shift of the perspective of how we look at AI based on the Rosenblatt model [13] of neuron and possible more generative approach for the robotic system management, for example, locomotion management with locomotion patterns of mammals.

Conclusions

In this work, we reviewed the three models of neurons that could be used as the foundation for the real-time neurosimulation. Previously we presented the ESRN model [10] that could be used for the real-time simulation of the spinal cord circuitry [11]. We also presented perspective on the use of the real-time neurosimulations for medical (neuroprosthetics), AI and robotic purposes.

Acknowledgements

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TOWARDS HARDWARE IMPLEMENTATION OF HIGH-DIMENSIONAL BRAIN

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The concept of a high-dimensional brain relies on the massive processing of data by high-dimensional neurons. It aims to answer the long-standing question: Why are neural networks (biological and artificial ones) so effective in many tasks? Recent evidence suggests that the answer may be in a specific advantageous interpretation of high-dimensional data. In contrast to the prediction made by the "curse of dimensionality" and false-negative expectations, some data analysis methods work much better in high-dimensional spaces. This observation motivated the rise of the theoretical concept of "blessing of dimensionality" [1]. Moreover, in the Medial Temporal Lobe, small neuron groups, or even single cells, can implement complex cognitive functions, such as generating abstract concepts (e.g., a Jenifer Aniston neuron).

Recently, it has been shown theoretically that assemblies of dynamically simple, but high-dimensional neurons, can be an effective tool for solving essentially high-dimensional problems that often defy treatment with standard methods [2,3]. This simplicity revolution opens a new venue for implementing advanced data analysis algorithms in hardware. A strong candidate for a breakthrough in this area is memristive technology, which allows building arrays of trainable artificial synapses on a chip [4].

In this communication, we overview theoretical bases behind ensembles of high-dimensional neurons and approaches to their hardware implementation with an eye at a functional simulation of the human hippocampus [5]. The discussed architectures focus on the novel electric element, the memristor. We show how the theoretical problem of processing complex high-dimensional data in AI systems can be reduced to learning in relatively simple neural networks based on memristive devices with rich internal dynamics. Thus, the proposed approach exploits the revolution of simplicity in neurosciences and offers the possibility of building devices with potentially complex cognitive abilities.

Acknowledgments

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NANOCOMPOSITE POLY-PARA-XYLYLENE MEMRISTORS FOR NEUROMORPHIC APPLICATIONS

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Introduction

The ever-increasing requirements for computing systems and limitations of the existing technologies demand novel solutions for the hardware designs. One way to lower power consumption and improve the efficiency of computing is to take inspiration from the brain and create so-called neuromorphic networks (NN) [1]. Implementation of each neuron and synapse, connection between neurons, of NN requires numerous transistors and consequently encounters scaling limits. Nevertheless, there are different ways to implement both; in this work we will address the memristor, an attractive candidate to mimic synapse due to its ability to combine information processing and storage [1]. Typically, memristor is a metal/isolator/metal (MIM) structure, the resistive state of which can be altered by external voltage pulses and remain the same for a long time after the removal of the voltage. The plasticity of the memristor, meaning the presence of several stable resistive states and possibility of switching between them, and the possibility of the resistive state change according to biological spike-timing-dependent plasticity (STDP) learning rules add yet more similarities between the memristor resistive state and the biological synaptic weight [1].

At present, many materials, both inorganic and organic, are reported to display memristive effects. In order to utilize memristors in NN successfully they should meet all of the requirements such as good endurance of the device, plasticity and retention of the states, high ratio of high-resistance state (HRS) to low-resistance state (LRS) and low stochasticity of the resistive switching (RS). Despite an explosive growth of scientific interest to this field, an ideally suitable structure is yet to be found. A promising candidate is a memristor based on poly(para-xylylene) (PPX, parylene) [2]. The stochasticity of the PPX-based memristor RS can be reduced by introducing metal nanoparticles into the PPX layer (e.g. PPX-Ag) or extra layers such as graphene [2,3]. Although PPX-Ag memristors have already been studied to some extent, there is still no clear understanding of the composition and fabrication parameters influence on the memristive characteristics, which is crucial for their application in NN. Moreover, the possibility of the resistive state update according to STDP learning rules for these structures has not been demonstrated yet. Therefore, the objective of this work was to address previously mentioned questions and to conclude whether the PPX-Ag based memristors are suitable for NN.

Methods

The memristive sandwich structures were fabricated as follows: PPX–Ag nanocomposite layer (fabrication method is discussed elsewhere [2]) was deposited onto a glass substrate covered with an indium-tin oxide (ITO) layer, which played the role of the bottom electrode, while the top electrode was made by thermal deposition of silver through a 0.2×0.5 mm^2 shadow mask. Five sample series with the volume fraction of the Ag nanoparticles (NP) 3%, 6%, 9%, 12% and 16% were fabricated. For each NP concentration three samples with different post-fabrication annealing conditions were made: with no annealing, annealing at 100° for 6 hours and annealing at 250° for 2 hours.

The memristive characteristics were measured via the Cascade Microtech PM5 analytic probe station. Voltage pulses were applied to the top electrode from the National Instruments PXIe-4140 source, while the bottom electrode was grounded. The microstructure of PPX–Ag film was studied using a Titan 80-300 transmission/scanning (TEM/SEM) electron microscope (FEI).

Results

The memristive structures with five different Ag NP percentage compositions were studied. The most stable RS were demonstrated by the memristors with 6% and 9% of Ag NP, while the others demonstrated unstable or no RS. The 6% and 9% memristors demonstrated current-voltage characteristics, which are typical for ECM memristors, good plasticity and retention. Moreover, the annealing of these memristors decreased the stochasticity of the RS even more and increased the ratio of HRS to LRS, which is significant for NN

implementation. This improvement can be explained by the increase of the NP size after the annealing and consequently stronger electrical field concentration. At the same time after annealing the distance between NP increases, which explains the higher ratio of HRS to LRS.

In order to demonstrate the possibility of training PPX-Ag memristors according to STDP learning rules, triangular voltage pulses were used as the pre- and postsynaptic spikes and applied to the top and bottom contacts. The optimal values of the amplitude and duration of spike pulses were found. The STDP window, the dependence of the conductance change on the time between the spikes, was obtained which proves the possibility of the resistive state update using biologically plausible algorithm. Moreover, a mathematical model, describing the obtained STDP windows, was made. Based on this model 12x2 NN was created and trained to process medical dataset, i.e. relying on the input data, resolve whether the patient would decease after the heart failure.

In summary, the nanocomposite PPX-Ag memristors demonstrated characteristics suitable for NN application.

Acknowledgements

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DEVELOPMENT AND COMPUTATIONAL SIMULATION OF THE BIOMORPHOUS DRIVER OF A FISH-LIKE ROBOT

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Abstract

This article presents a new prototype of a biomorphic propulsion device for an underwater fish-like robot. The propulsion device is based on a combination of an elastic plate with a tail fin attached to it and movable cables that act as muscles. The propulsion device imitates the swimming of fish with the tunniform principle of locomotion. Successful tests of the propulsion device mounted on a fish-like robot were carried out. When designing the propulsion device and the body of the fish-like robot, biological references were used, as well as optimization in the software of finite element analysis.

Key words

Actuator, Fish robot, Modeling, Bioinspiration, Swimming, Autonomous underwater vehicles.

Introduction

The colossal length of the world's ocean, its importance as a transport route and the need to monitor and research its depths set the task of creating autonomous underwater vehicles. At the same time, the installation of classic propulsions on drones, such as propellers or water jets, cannot always provide the required level of energy efficiency and maneuverability. At the same time, the biodiversity of aquatic organisms and the degree of their adaptability to the aquatic environment indicate the possibility of imitating the natural principles of movement under water when developing propulsion devices. The creation of biomorphic underwater propulsion

devices can reduce the energy consumption for movement, as well as reduce the negative consequences of intervention in the environment. The mode of movement common to most fish doesn't create the noise typical of propellers and is natural for aquatic fauna.

Methods

Bionics involves the use of natural mechanisms and principles in the design of mechanical devices. In our case, fish became the biological prototype. There are several types of locomotion characteristic of different fish species. Since the main area of application of the propulsion device will be slowly moving or stagnant sea water, the tunniform principle of locomotion was chosen. The movement of the fish is an oscillation with increasing amplitude. We have designed a propulsion device that simulates the movement of fish (Fig. 1). The propulsion device has the shape of a tail and consists of a flexible plate with a tail fin attached to it. On both sides of the flexible plate, there are rods that deform it when the servo rotates. To give an additional degree of freedom, the tail fin is mounted on a spring-loaded hinge. The rods are sealed with silicone bellows.

A fish-like robot was developed to test the propulsion device. When designing the robot, a fish of the mackerel family, Pacific Bluefin Tuna, was chosen as a reference. Based on the photographs, a 3D model was built, then it was adjusted for the equipment that should be placed in the case.

In parallel, the task of optimizing the movement of a fish-like drone in the ANSYS software system using finite element method was performed. A prototype of a biomorphic propulsion device was developed to simulate the movement of a fish, which will later be used to verify the computer model.

A number of experiments have been carried out to test the swimming of a fish-like robot in a pool. The robot was placed in the pool, then a control command was sent from the computer via WI-FI. The control instruction started the motions of the propulsion unit with a given frequency and amplitude of tail flaps. In different series of experiments, different initial parameters of the frequency (from 0.5 to 7 Hz) and amplitude (from 20 ° to 80 °) of the flaps were set.

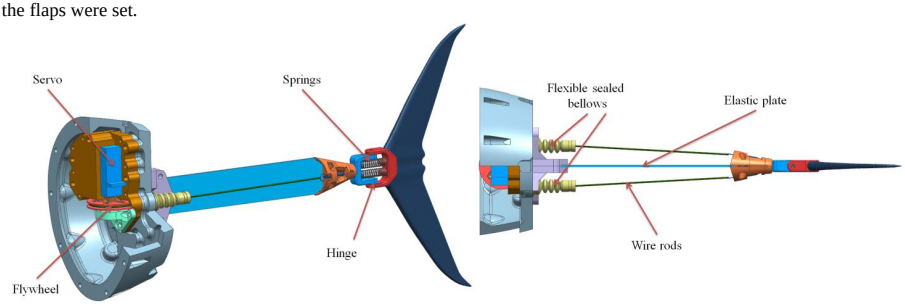

Fig.1 A prototype of a biomorphic mover

Results

We have developed a biomorphic propulsion device and a fish-like robot simulating fish swimming. The propulsion device and robot were manufactured and tested in a laboratory environment. Their operability was confirmed, as well as the possibility of using the propulsion device for maneuvering (turns in the horizontal plane).

Discussion

The results showed the possibility of using a biomorphic propulsion device as the main vehicle for a fish-like robot. The use of such propulsion devices opens up broad prospects for improving underwater robots. In further experiments, it is planned to use methods for visualizing fluid flows, such as visualization with dyes and the use of digital tracer visualization of flows.

Acknowledgements

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DIMENSIONALITY REDUCTION OF PLACE CELLS NEURAL ACTIVITY IN MICE

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Aims

The concept of so called "neural modes" gains popularity in computational neuroscience [1]. The activity of many neurons can be described in terms of the high-dimensional neuronal "state space", where each coordinate usually describes the activity of a single cell. One would expect that the number of degrees of freedom for a system of neurons is equal to the number of cells in it. However, it was shown in experiments that real activity of neural population occupies only a small part of such "state space" [2-4]. Thus, dimensionality reduction of input data is used to obtain its low-dimensional representation. The exact meaning of the axes of such a new low-dimensional space is still poorly investigated for neurodata. We can expect them to encode "integral" characteristics reflecting the activity of the population as a whole. The goal of this work was to obtain information about the behavior of the animal from the activity pattern of place neurons only.

Methods

The place neurons of the mouse hippocampus, which are responsible for encoding the animal's spatial location, were chosen as the object of study. During the experiment, the mouse moved freely through the environment, its coordinates and behavior were recorded using video tracking. The experiment was performed for a circular arena with 3 restricted zones in order to create non-trivial topology of the explored space. Using Inscopix NVista HD miniscope, the calcium fluorescence of hippocampal CA1 field neurons was recorded, which was then transformed into the calcium signal of individual cells. Nonlinear methods of data dimensionality reduction, including laplacian eigenmaps [5] and isomap [6], were applied to the multidimensional calcium signal from the population of recorded cells.

Results

The first two axes of the low-dimensional space got the meaning of the coordinates of the mouse in the physical environment it was exploring (with the accuracy of rotation by a fixed angle). It is important to note that the algorithm did not receive any information about the real position of the mouse as an input. Thus, the coincidence of the first two coordinates of the new space with the real position of the animal is explained by the similarity of the vectors of neural activity recorded at different times, but in the same location of the environment. We are currently working on figuring out the meaning of the remaining several coordinates of the low-dimensional representation.

Conclusions

This work is important for understanding the principles of internal information coding in the hippocampus. The study of the space of neural states is important for the reconstruction of the brain's "internal representation" of external stimuli.

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TURBULENT MODEL DEVELOPMENT FOR SLOPE FLOW SIMULATION USING TBNN

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Slope flows are flows on mountain slopes such as avalanches, mudflows, landslides, and others. These flows are turbulent multiphase flows of non-Newtonian media. Existing turbulence models describe this type of flow poorly and require refinement and calibration. The development of a turbulent model can be carried out in several ways, one of the most accurate of them is using direct numerical simulation (DNS). That is a very detailed eddy-resolving simulation carried out with the help of a supercomputer. To develop turbulent models, it is required to process the results of DNS modeling, which are a large amount of data containing such information about the flow as velocity, pressure, density, viscosity and other flow parameters in the entire set of points of the computational domain at all times. Tensor basis neural networks (TBNN), which are considered in this work, are best suited for processing data arrays and constructing new dependencies when describing a turbulent model.

In this work, a two-stage calibration of the turbulent model is carried out. First of all, the optimization of the coefficients of the existing turbulent model is carried out. Next, an expression is constructed for the anisotropic normalized Reynolds stress tensor. The scheme of work is shown in Fig. 1.

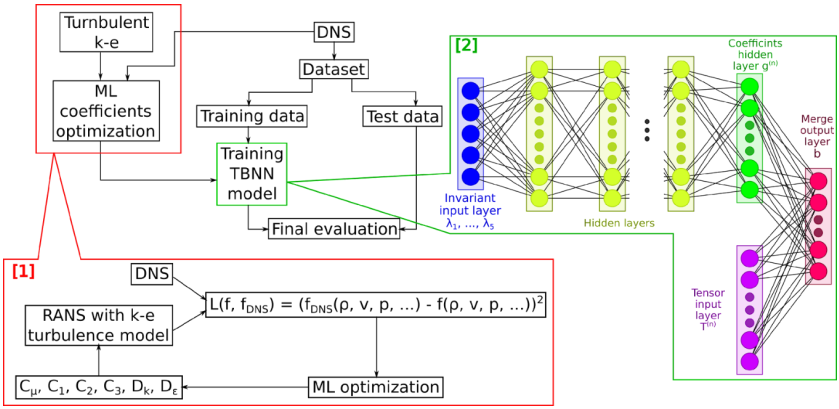

Fig.1. Workflow scheme

Calibration of the turbulent model is planned using the following optimization algorithm based on reinforcement learning: 1. Training the neural network based on a number of calculations carried out using the RANS model with the k - ε turbulence model with different values of the constants; 2. Obtaining new values of the coefficients of the turbulent model using machine learning; 3. Calculation of flow hydrodynamics using a turbulent model with coefficients obtained using machine learning; 4. Additional training of the algorithm using the obtained data from the calculation of flow hydrodynamics.

To obtain an expression for the anisotropic normalized Reynolds stress tensor, it is proposed to use a special neural network architecture based on a tensor basis. The input data of the neural network is based on 10 basic isotropic tensors T_i and their invariants λ_i, which are functions of the dimensionless Reynolds-averaged strain rate tensor s and the dimensionless Reynolds-averaged rotational velocity tensor r, these are all sorts of linearly independent combinations of s and r. At the output of the neural network, the corrected tensor of the normalized Reynolds stress tensor b is obtained, represented as a dependence on the tensors T_i and their invariants λ_i.

As a result of the study, a calibrated turbulent model was obtained that is suitable for describing multiphase flows of non-Newtonian fluid on slopes. Using the obtained turbulence model, a simulation of the experiment of the University of Iceland with the descent of a flow in a flume with a complex of protective structures was carried out; a decrease in the discrepancy in the value of the volume of the flow retained by the barrier structures in comparison with the experiment was obtained (a more accurate assessment of the effectiveness of the complex of protective structures was obtained). Modeling of the 22nd avalanche center on the Yukspor mountain of the Khibiny mountains was carried out using a calibrated turbulence model.

The turbulent model obtained using TBNN made it possible to increase the accuracy of assessing the avalanche-hazardous zone, the effectiveness of protective structures, and obtain more accurate flow characteristics.

Acknowledgements

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NEURAL NETWORKS FOR PREDICTING THE ICE SHAPE ON AN AIRFOILS

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Icing is a dangerous phenomenon in aviation, transport and energy. From the point of view of a physical process, this is a complex phenomenon that includes gas dynamics, dynamics of particles, liquid film dynamics, thermodynamic and phase transitions. The shape of the ice depends on various conditions: wind velocity, the temperature of the flow, size of a droplet in air, quantity of droplets, and the time of influence of the flow on the airfoil. Flight experiments for researching icing are expensive and depend on weather conditions. Laboratory experiments require special facilities and climate wind tunnels. Numerical simulation of this process requires special software and supercomputer resources. The aim of this study is to develop a special neural network that can predict ice shape on an airfoil.

Previously, research has been carried out using computational fluid dynamics and neural networks to simulate the ice formation process on the wing airfoil. A study was carried out of several neural networks architectures [1].

To study the change in the wing airfoil during icing in [2], an algorithm was used that involved two conformal mappings, namely, the investigated profile into a parabolic profile and a parabolic profile into a straight line. In this case, the shape of the frozen ice was presented as a perturbation of this line. The perturbation form was specified by a Fourier series or using wavelet functions [3,4]. The number of coefficients in the expansion and their values were the objects of prediction of the neural network.

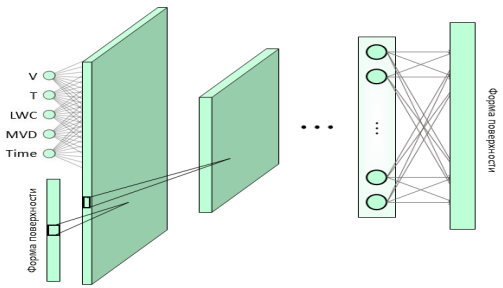
The following 5 parameters were used as input parameters for the neural network:

- atmospheric conditions (temperature T and pressure p),
- flight parameters (speed V),
- droplet diameter d,
- density or water content of drops ρ,
- drop time t.

When studying the coefficients of the function approximating the shape of frozen ice, it was taken into account that their number should not greatly exceed the number of input parameters, otherwise the training time of the neural network would increase and the accuracy of the predicted results would decrease.

For validation, the results of the NASA experiment and the results of CFD modeling in the LEWICE package were used.

We counted the ice shape for 5 different airfoils using iceFoam solver, developed in ISP RAS. A neural network needs sampling and labeled data. We used calculation data for 50 airfoil cases (NACA 0012, GLC-305, Business jet, General aviation, Commercial Transport) and 1000-time steps. A spectrum of neural network architectures (CNN, RNN, RBNN) for the problems of predicting ice build-up on the wing airfoil is considered. An example of CNN architecture is shown on Figure 1. We used 5 parameters and ice forms as an input data.



Trained neural networks can be used for fast predictions of ice shapes on an airfoil in minutes instead of hours and days that requires numerical and laboratory investigations.

Acknowledgements

This research was supported by the Ministry of Science and Higher Education of the Russian Federation, agreement No 075-15-2020-808.

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ASSOCIATIVE LEARNING IN STRUCTURED SPIKE NEURAL NETWORKS

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Learning and memory are basic cognitive functions. The main mechanism that implements these functions in the brain is believed to be synaptic plasticity - the ability of interneuron connections to change the structural and functional state depending on the previous neuronal activity. Various approaches are used to explain the principles of synaptic plasticity, and therefore memory formation and learning. In particular these approaches include growing neural networks *in vitro*, developing its mathematical models and computer simulations. However, the issue of network interaction is still insufficiently covered, despite great success in understanding the mechanisms of neuronal interaction at the cellular level. In addition, the problem of implementing associative learning in neural networks *in vitro* remains unsolved. In this context, simulating the interaction of neural networks seems to be an actual approach for solving the indicated problems.

Aims

The purpose of this work was to implement associative learning in the form of classical (Pavlovian) conditioning in structured spiking neural networks (SNN) consisting of several subnets, and to demonstrate learning using a neuro-robot.

Methods

We used Izhikevich's model to describe the neuron dynamics. Synaptic plasticity was represented by Spike-timing-dependent plasticity (STDP). A simulated network consisted of two subnets, including 200 neurons each. The ratio of excitatory neurons to inhibitory neurons for the first/second subnet was 2:1/1:1. All interneuron coupling in the first subnet and excitatory connections in the second subnet were local, and inhibitory connections in the second subnet were distant.

The SNN controlled a neuro-robot with two pairs of ultrasonic and touch sensors. Touch sensors stimulated the parts of the SNN responsible for motor functions, and ultrasonic sensors were mapped with associative functions. Activation of the sensors triggered the corresponding stimulation. In turn, when motor neurons were activated, the neuro-robot changed the trajectory of movement to avoid an obstacle. To test the

training, we created an experimental arena with obstacles. The neuro-robot with varying degrees of training moved in the arena for 5 minutes. At the same time, we recorded the number of collisions with obstacles.

Result

Generally, classical conditioning binds a conditional stimulus (CS) with an unconditional stimulus (US). The US always evokes a response in the nervous system, whereas the CS initially does not. After several presentations of the US and CS together, the nervous system starts responding to the CS alone. At the beginning of the training, the connections between the subnets have the identical low efficiency (the identical small weights in terms of the model). When the ultrasonic sensors are activated, a part of the CS-subnet receives stimuli. After a while, the robot touches an obstacle and the US-subnet is activated. At the same time, we observe a gradual potentiating of connections between the subnets, since the CS- and US-subnet is activated together. Note, that during training, the connections that provide the shortest pathway of the spikes are potentiated. At that time alternative connections between subnets are depressed. As a result of these synaptic rearrangements, the network activity changes: in response to CS, the network shows selective responses the same as in the case US. Accordingly, when an obstacle was approaching from the left or right sides (CS), the trained neuro-robot goes around an obstacle (an unconditional response) without collisions.

After training and testing, we swap the ultrasonic sensors, simulating changes in the environment. As a result, the robot begins to make mistakes, hitting obstacles instead of avoiding them. However, there is a joint activation of other parts of the SNN, compared to the previous case. As a result, after a certain time, new associative pathways are formed, connecting CS and US. The network again shows a selective response to CS. Thus, the robot is relearned and can again go around obstacles without touching them.

In order to assess the quality of training, we introduce a coefficient of learning quality (Q), based on the weights of connections between subnets. Q is defined as the ratio of the weights of the connections that are expected to potentiate in the learning process to the sum of all connections between subnets. As a result of testing, we find an inverse relationship between Q and the number of collisions. When using untrained SNS, the neuro-robot makes significantly more collisions than when using trained SNS (14.08 ± 3.81 vs. 2.93 ± 1.8). Thus, the proposed coefficient Q, calculated on the basis of the weights of the connections of learning neurons, really characterizes the quality of learning recorded at the “behavioral” level.

Conclusion

In this paper, we simulate classical (Pavlovian) conditioning with a robot controlled by SNN. Associative learning was based on the interaction of interconnected subnets of SNN and changing the connections between subnets. We showed that after training, the neuro-robot allowed collisions with obstacles significantly less than in the initial period. To assess the quality of training, we proposed a learning quality coefficient calculated based on the values of the weights of connections between subnets. We showed that the value of the coefficient has a negative correlation with the number of errors made by the neuro-robot. Thus, we implemented associative learning in SNN and simulated it at the synaptic, network and behavioral level.

Acknowledgements

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COMPUTATIONAL NEUROSCIENCE

COMPUTATIONAL NEUROSCIENCE is an interdisciplinary field for development, simulation, and analysis of multi-scale mathematical models to investigate brain function.

Section topics include, but are not limited to:

- Dynamical systems in neuroscience
- Single neuron modeling
- Neuronal ensembles and synchronization
- Synaptic plasticity
- Spiking neural networks
- Memory, cognition and learning in computational neuroscience
- Information theory and neural coding
- Applications of neurocomputing
- Brain signal analysis: methods and applications

BURSTING ACTIVITY IN A MODEL OF NEURON-GLIAL INTERCATION

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In this talk, we propose and discuss new phenomenological model of neuron-glial interactions [2,3] based on short term synaptic plasticity (STSP) [1] and recurrent connections in order to study bursting activity observed in biological experiments. We found that neuron-glial interactions can produce bursting temporal patterns and therefore play crucial role in understanding of the complex dynamics of neuronal networks.

Our 4-dimensional STSP-based model of neuron-glial interactions has the form

E=-E+αln 1+eJuxE+I0, x=1-xD-uxE, u=Uy-uf+Uy1-uE, y=-yy+βHx, (1)

where E(t) is a mean firing rate of a population of identical excitatory neurons, x(t) is an overall fraction of available neurotransmitters, u(t) is the release probability of available neurotransmitters, and yt is the concentration of the gliatransmitter. Functions Uy=U0+U01+e-50(y-0.5) with parameters U0, U0, and Hx=11+e-20(x-0.9) are sigmoidal functions modelling the activation in u and y, respectively. Parameters, , J, , D, f and y are positive constants, and I0 is a global inhibition considered here as a bifurcation parameter.

Dynamically, model (1) can demonstrate a rich set of temporal patterns, from simplest ones, such as quiescence (corresponding to a stable equilibrium) and tonic spiking (corresponding to a one-loop limit cycle), to regular and irregular bursting (corresponding to multi-loop periodic orbits and irregular complex motions). Bifurcations connected with this transition were studied in detail.

It was obtained numerically that increase in I0 leads to increase in number of spikes per burst [see Fig.1(a),(b)], and beyond some critical value of I0*≈-1.7392 the bursting regime is eventually transformed into tonic spiking [see Fig.1(c)].

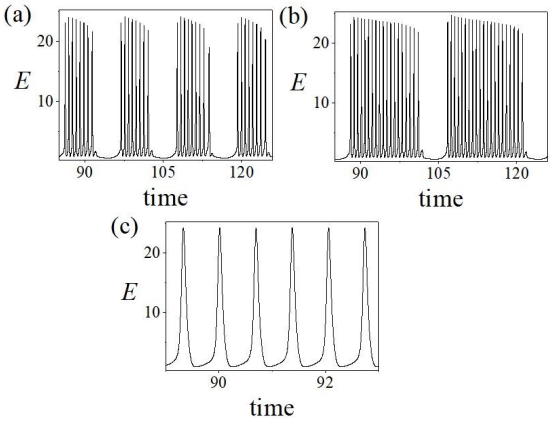

Fig.1. Time series of E(t) for different values of I0. For I0=-1.7415, a burst consists of 8-9 spikes on average [the panel (a)]. For an increased value of I0=-1.74, bursts have a longer period (a larger number of spikes per burst) [the panel (b)]. For I0=-1.7385 model (1) demonstrates tonic spiking [the panel (c)], into which the bursting regime was eventually transformed at critical value of I0=I0*. Other parameters: τ=0.013, α=1.5, J=3.07, d=0.15, f=1, β=0.4375, U0=0.305.

Acknowledgements

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TOWARDS MORE BIOLOGICALLY PLAUSIBLE CPG MODELS

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Aims

Central pattern generators (CPGs) are small neural circuits that can produce rhythmic patterns of activity, including in the absence of an external drive [1,2]. Their fundamental role is determining multiphase locomotion in diverse invertebrate and vertebrate animals. In a polymorphic CPG, activity can be modulated by hierarchically higher areas, thus prompting gait switches [3]. This control action is integrated into most CPG models by manipulating synaptic conductances [4-7], while, in real CPGs, changes of conductances are likely due to long-term synaptic plasticity, which can hardly result in quick gait switches. Our goal is to develop biologically plausible CPG models by integrating short-term plasticity mechanisms coordinating phase lags among constituent neurons as their spike frequency varies along with sensory or external drives.

Methods

One pivotal building block of many CPGs is the half-center oscillator (HCO), which is formed by two pools of neurons reciprocally inhibiting each other to stably produce rhythmic alternation [8]. In [9] we proposed a generalized HCO (gHCO) model with integrated short-term synaptic plasticity. In the gHCO, the neurons are coupled by both inhibitory and excitatory synapses. Some of those are slow synapses with post-synaptic potential (PSP) summation whose strength correlates with spike frequency variations in presynaptic cells, while others are fast synapses without PSP summation whose conductance is not affected by the spike frequency. Such a mixed circuitry is supported by the evidence of PSP summation observed in some synapses of biological CPGs [10] and by the absence of PSP summation in fast synapses [4]. We employ a Hodgkin-Huxley (HH) type model of an endogenous burster [11], in which the mean intra-burst spiking frequency can be controlled through an external current Ic. The gHCO concept is based on a simple principle: since the strength of the fast synapses does not depend on spike frequency, but the strength of the slow synapse does, changing the spike frequency through Ic allows one to modify the ratio between inhibition and excitation strengths and thus influences the phase lag between the neurons. For certain values of Ic excitation prevails, and the neurons tend to burst in sync, for other values of Ic inhibition prevails, and the neurons tend to burst in alternation [9].

In our ongoing research, we employ the proposed gHCO as a building block for a CPG model to reproduce quadruped gaits. We proposed a minimalistic 4-cell CPG model [6] representing the reduction of a 40-cell physiologically-grounded CPG model of the mouse locomotion [12].

Results and Conclusions

Following a design strategy that merges the methods proposed in [6] and [9], the proposed CPG circuit produces stably three rhythms modelling bound, trot and walk gaits. These results shown in Fig.1 are obtained with a modified version [9] of the first-order synapse model [13], as a greater spike-frequency-dependent variation of synaptic activation is warranted.

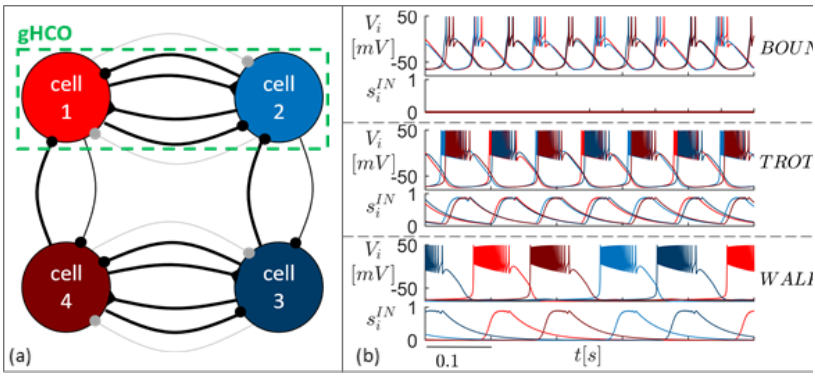

Fig.1. (a) 4-cell CPG with inhibitory (●) and excitatory (<) synapses; inhibitory synapses in the gHCO are slow, all other synapses are fast. (b) Membrane voltage Vi of all 4 neurons (color code as in panel a) and activation of the slow inhibitory synapse siIN(color code as presynaptic neuron) for the obtained gaits; connectivity and synaptic weights are never varied, different gaits are obtained for different values of the incoming current Ic.

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LOCALIZED COHERENT STATES IN A POPULATION OF NEURON-LIKE ELEMENTS WITH NON-LOCAL COUPLING

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Introduction

Understanding the fundamental mechanisms governing fluctuating oscillations in large-scale cortical circuits is a crucial prelude to a proper knowledge of their role in both adaptive and pathological cortical processes. Neuroscience research in this area has much to gain from understanding the Kuramoto model, a mathematical model that speaks to the very nature of coupled oscillating processes, and which has elucidated the core mechanisms of a range of biological and physical phenomena [1].

The Kuramoto model specifies global (all-to-all) coupling amongst system oscillators. Whilst this may be a reasonable approximation in a small network of densely connected neurons, it is certainly not true for large populations of neurons distributed across the cortical sheet. In this case, the coupling amongst the oscillators should be spatially embedded. Put differently, it should allow for the presence of time delays between distant subsystems and accommodate reduced coupling strength with distance. Here we take this into account due to nonlocal coupling and the finite time of the diffusion process. The focus of this paper is aimed at localized coherent states.

Model

We consider a medium of identical non-locally coupled neuron-like elements, defined by the phase φ(x,t) and distributed on a ring of length L:

tφ=ω+ImHe-iφ+α,tH=xx2H-
H+eiφ, 1)

where is a natural frequency of the rotation, is a phase shift, H(x,t) is an auxiliary field determining the coherence degree of the neighboring oscillators. Parameter indicates the characteristic time scale of the function H(x,t) [2].

Results

The aim of this work is to study a localized coherent state (see Fig.1), which is a small coherent region among an asynchronous background in a long media. Here we find such states as a homoclinic trajectories of an auxiliary system of third-order differential equations. It is shown that there is a range of values of control parameters where the studied mode is stable. Regimes of soliton turbulence and spatial-temporal intermittency are observed with the loss of stability of a localized coherent state.

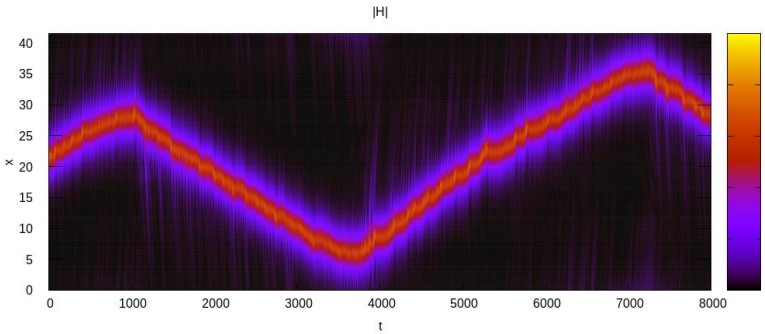

Fig.1. Localized coherent state. Spatiotemporal diagram of absolute values of the complex average field H(x,t) for $L = 42$, $\omega = 0.45$, $\alpha = 1.62$, $\tau = 0.5$

Acknowledgements

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EXPERIMENTAL INVESTIGATION THE DYNAMIC OF TWO HARDWARE NEURON MODELS CONNECTED THROUGH MEMRISTIVE ELEMENT

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While neuroscience is one of the most dynamic branches of interdisciplinary science it still has a lot of unsolved problems in the field of information processing principles.

In this work, we studied the behavior of two neuron-like generators connected through the memristive element.

We used Neuron-Like Generator based on a phase locked loop system with a band pass filter (PLL) [1-2]. A second-order memristor model based on Chua's memristor [3-5] was used as a model of synaptic connection.

In the first experiment, a nonlinear dependence of the memristor conductivity on incoming spike frequency was obtained. In this experiment a hardware model of the neuron-like generator was connected to memristive circuit.

Memristor conductivity increases only up to 70% of the maximum value a spike frequency of 1.6 kHz, while, this conductivity increase reaches 100% with the same number of active spike at a frequency of 10 kHz. When using burst or chaotic modes of neuron-like generator, the changing the memristor conductivity occurs unevenly in response to spikes and strongly depends on the inter-spike intervals in the burst. Such dynamics of the memristive element is qualitatively similar to frequency dependent or short-term synaptic plasticity.

In the second experiment, synchronization of two neuron-like generators connected through a memristive element was found. Synchronization of two coupled neuron-like generators is interim in nature and strongly depends on the current state of the memristive element.

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SYNCHRONIZATION BETWEEN PROCESSES OF LOW-FREQUENCY REGULATION OF BLOOD CIRCULATION IN AWAKE AND SLEEP

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Many works indicate the importance of studying the processes of autonomic control loops of blood circulation for understanding the fundamental principles of the functioning of the cardiovascular system [1] and solving applied problems of medical diagnostics [2]. The aim of this study is to study the effect of the state of the central nervous system (awake state and different stages of sleep) on phase synchronization between the processes of baroreflex control of mean arterial pressure and autonomic control of the heart rhythm, which have own frequencies of about 0.1 Hz.

Low-frequency components of oscillations of blood pressure (BP) and cardiac interbeat intervals (RR-intervals) are often used as a source of information about these processes. We used time series from 30 healthy subjects in the CILA database [3] in awake state, deep sleep and REM sleep. For each subject in each state, we calculated the total percentage of phase synchronization S [4] and its level p of statistical significance. The S measure has the meaning of the relative time of the synchronous behavior of the oscillations under study. The level of statistical significance was calculated using surrogate data [5]. The S measure was considered statistically significant if $p < 0.05$.

The results of the study showed that the studied processes, both in awake state and sleep state, demonstrate intervals of phase synchronization. Moreover, the state of the central nervous system changes the ability of control processes to adapt to each other's oscillations as a result of interaction. The longest relative time of synchronous behavior of the processes and biggest total percentage of phase synchronization were revealed in the state of REM sleep, compared with awake state and NREM sleep.

Thus, the S measure proposed by us may turn out to be a useful tool in the development of methods for classifying sleep stages in polysomnographic studies.

Acknowledgements

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INTEGRATION OF POSTURAL CONTROL WITH BRAIN-COMPUTER INTERFACES

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While many types of brain-computer interfaces (BCIs) have been developed over the years, EEG-based BCIs represent the most popular design because of their non-invasiveness and ease of implementation to real-life applications. The most popular designs here are external stimulus-based P300 BCI [1] and endogenous motor imagery-based BCIs [2].

EEG-based BCIs have been explored in both healthy subjects and patients [3, 4, 5]. In a typical experiment, a subject is asked to inhibit any overt behavior, so that BCI control is "pure". While the desire to develop such fully independent BCIs is understandable, it is usually impossible to keep neuronal activations confined to the brain and not spreading to the lower levels of the nervous system, such as the spinal cortex. Thus, during the preparation of a movement and in the absence of any overt behavior, modulations are detected in the spinal cord interneurons [6]. Although such activation of the structures connected directly to muscles is often neglected in BCI literature, it could be of interest to both fundamental science and practical BCI applications.

In this work, by using simultaneous recording and following analysis of EEG, EMG and posturographic data in healthy subjects, we explore postural reactions that accompany preparation and execution of voluntary movements and performance on BCI tasks to augment BCI control with additional features. We explore a range of postural responses that serve to maintain balance. This research is novel. Postural control has been studied extensively [7, 8, 9], but not in conjunction with BCIs. We show that postural reactions could be quite useful for monitoring the performance in BCI tasks and developing hybrid BCIs that incorporate information about postural control. Thus, in our BCI design we incorporate imagined movements that cause postural adjustments [10, 11, 12, 13, 14]. We suggest that anticipatory postural adjustments that accompany EEG modulations during voluntary and imagined movements can be utilized in practical BCIs that strive to restore synergy between the brain activity and postural responses.

Acknowledgements

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ANALYSIS OF DIRECTIONAL COUPLINGS BETWEEN INFRA-SLOW OSCILLATIONS OF BRAIN POTENTIAL AND CARDIAC INTERBEAT INTERVALS

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The normal functioning of the human body requires the coordinated work of a huge number of complex nonlinear systems of high dimension: cardiovascular, respiration, autonomic control, cortex activity etc. The study of the coupling structure between such systems has great fundamental physiological importance [1].

Purpose of the work is to identify the directional coupling between the structures of the brain and the autonomic control of blood circulation, to analyze the changes in these coupling in sleep and in wakefulness.

We used simultaneous signals from parietal leads C3, C4 and electrocardiogram (ECG) of 5 healthy subjects with an average level of physical activity from the SIESTA database [2]. We have used segments of awake state, REM-sleep and non-REM (NREM, slow-wave) sleep. Sleep stage marking was carried out by the recommendations of Rachtsaffen and Kales [3].

An equidistant sequence of RR-intervals was extracted from the ECG using the recommendations [1].

We calculate the strength of the directional coupling between the studied processes using the simultaneous oscillations from EEG and RR-intervals in LF-band. We used the method that was proposed in [4].

Assessment of the directional coupling between the studied processes begins with the identification of instantaneous phases of the signals in the corresponding frequency ranges.

To identify the phases, we filter signals in LF-band. Then, we calculated the instantaneous phases for RR-intervals – xt and EEG – yt , using the Hilbert transform [5]. The dynamics of the phase signal was approximated using the first-order phase oscillators:

dxtdt=wx+Kxxt,yt-
Δy→x+xt, 1)

where x,y - first and second systems (x≠y), wx - parameters that determine the angular vibration frequencies, Kx - defines the coupling between the *x* and *y*, Δy→x - delay between the systems, xt - white zero-mean noise. Then we create the model of the phase increment over the period of τ seconds:

xt+τ-xt=Fxxt,yt-
Δ,ax+xt, 2)

where Fx is the third-order trigonometric polynomial function, ax - the vector of its coefficients, Δ - trial delay, xt – model residuals. From time series we estimated the coefficients ax and calculated the coupling strengths in direction from *y* to *x* for a trial time-delay of Δ:

Gxy2(Δ)=∫∫02πFx(Δ)

y2dxdy 3)

The coupling coefficient is normalized to the variance of the instantaneous phase signal of the acting system. Thus, for example, the values of Gxy2(Δ) characterize what fraction of the variance of the signal phase oscillations RR-intervals can be described using the values of the signal phase oscillations EEG.

Figure 1 shows the indices Gxy2 and Gyx2 averaged over the experimental ensemble. It shows the bidirectional coupling between EEG and RR-intervals for the awake state and different sleep stages. One can found a decrease of indices while going from wakefulness to sleep

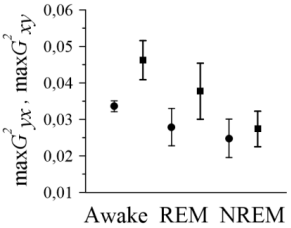

Fig.1. Indices Gxy2 and Gyx2 averaged over the experimental ensemble. Circles are for the direction of coupling from EEG to RR-intervals (Gxy2), squares are for the direction of coupling from RR-intervals to EEG (Gyx2). The whiskers corresponds to the standard error values.

During the analysis of time series of infra-slow EEG oscillations and RR-intervals of healthy subjects (SIESTA database), it was shown that the coupling coefficients, on average, decrease as they fall asleep. It was also shown that the coupling asymmetry (the ratio between the values of the directional coupling coefficients) in the LF-frequency band depends on the physiological state of the subjects and differs in awake state, REM sleep and S3 NREM sleep stages. The results obtained make it possible to better understand the features of the interaction of the higher nervous centers and elements of autonomic control of blood circulation. The results are seems promising for the development of methods for classifying the sleep stages.

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DETECTION OF SPONTANEOUS ACTION POTENTIALS IN EXTRACELLULAR RECORDINGS OF VISUAL CORTEX NEURONS USING EEG PREDICTORS FOR A MACHINE LEARNING-BASED APPROACH

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Spontaneous activity is known to be a characteristic feature of the vast majority of the neocortical principal cells including neurons of the primary sensory areas. The question of how spontaneous activity interacts with perception and encoding of sensory information remains open. In the present study, pyramidal neurons of the mouse primary visual cortex were recorded extracellularly under urethane anesthesia and simultaneous single-channel EEG recording was performed. To evaluate orientation and direction selectivity of the recorded neurons, mice were presented with visual stimuli consisting of moving sinusoidal gratings of different orientations displayed on a monitor. We noted quite regular bursts of generalized brain activity that were manifested in the recorded neuron as bundles of action potentials accompanied with a distinctive EEG pattern. Clearly, whenever such spontaneous activity shows up during visual stimulation, it is considered as noise, which significantly compromises the characteristics of the neuron's measured visual response. To eliminate this effect, we developed a machine learning-based algorithm that enables to identify EEG predictors of generalized spontaneous activity and next to "subtract" spontaneous (i.e. not evoked by visual stimulation) action potentials from the record. Predictor features were computed from the coefficients of discrete wavelet transform performed on extracted EEG snippets and the training dataset was fed into a support vector machine classifier. Thus, trained model was then used to detect spontaneous APs in the visual stimulation recordings. The experimental data obtained indicate that our algorithm can reliably detect action potentials that have been caused by generalized brain activity. Removal of action potentials of this origin from extracellular recordings obtained during visual stimulation allows for a more adequate estimation of parameters of neuronal receptive fields, in particular their orientation selectivity.

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EFFICIENT REDUCTION OF THE COLLECTIVE DYNAMICS OF NEURAL POPULATIONS WITH REALISTIC FORMS OF HETEROGENEITY

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The study of the collective dynamics of large heterogeneous populations is one of the topical issues in nonlinear science. Problems of this type naturally arise when modeling neural networks, in which natural frequencies, strength of coupling, bias currents, and other parameters may vary from one element to another. Surprisingly, very often the dynamics of such complex multidimensional systems turns out to be relatively simple. This gave a powerful impetus to the search for suitable reduction methods and to the construction of new low-dimensional mean-field models [1].

Here we are concerned with the collective dynamics of quadratic integrate-and-fire neuron network with an arbitrary distribution form of bias currents. We propose the efficient reduction technique that accurately describes the dynamics of a population of thousands of neurons with just a few macroscopic complex variables [2].

The first step is based on the Lorentzian ansatz, which allow us to obtain a closed set of integro-differential equations for globally coupled population of neurons. These equations describe the mean-field behavior and are exact in the thermodynamic limit. They remain valid for an arbitrary parameter distribution. Nevertheless, an explicit finding of the integral part is required. The idea we are developing is to use an approximation that allows calculating the integral using the residue theory, but having only a few poles. We use a series of approximations in the form of rational functions. Using the Gaussian distribution as an example allows us to obtain reduced system that show a good agreement with the macroscopic behavior of full neuron population.

Note that the method we are developing is not limited to the Gaussian distribution but applicable to an arbitrary distribution, which can be approximated by a series of rational functions, such as Padé approximants, Chebyshev-Padé approximants, or some others.

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INVESTIGATION OF WORKING MEMORY CAPACITY IN SPIKING NEURAL NETWORK

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Working memory refers to short-term storage and manipulation of information. In the delayed-response paradigm, a stimulus that is briefly presented to an animal has to be kept for several seconds until the execution of a task. Enhanced, stimulus-specific spiking activity has been observed during this delay period and is considered to be a neuronal correlate of WM [1].

We investigated a working memory capacity of a recurrent network based on neurons - threshold integrators. It is assumed that the item is maintained in the state of working memory by short-term synaptic facilitation mediated by an increased level of residual calcium in the presynaptic terminals of neurons that encode this element. Mathematical modeling of this mechanism has been carried out. The elements are loaded into working memory by external excitation of the corresponding neurons populations. Neurons encoding the same image have stronger connections than connections between different populations. Inhibitory and excitation are randomly connected, which leads to competition between different memories. All connections between excitatory neurons show enhanced transmission as described by the phenomenological model of short-term plasticity. Gaussian white noise is used as external currents.

The working memory capacity of the frequency model, depending on the temporal parameters of synaptic plasticity, was investigated in the paper [2]. We similarly investigated the influence of the parameters of the calcium level recovery time and the neurotransmitter recovery time on the number of saved items in the considered spiking network model. The results showed that with an increase in the recovery time parameter of the calcium level, the capacity value increases on average. An increase in the potentiated level of compounds from an excitatory neuron to an excitatory one leads to an increase in capacity on average. A decrease in the overall network activity due to a decrease in the mean value and variance of the external current leads to a decrease in the capacity on average.

A similar network model with overlapping connections is considered, when some of the neurons of the populations encoding the item have strong connections with other populations. The influence of overlapping populations of neurons in the network working memory model on the working memory capacity was investigated. The results showed that the dependence is similar to the dependence of the capacity on the parameters of synaptic plasticity of a similar network without overlapping ensembles.

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ACCESSING ATTENDED AND REMEMBERED LOCATIONS IN PREFRONTAL CORTEX USING DEEP LEARNING APPLIED TO NEURONAL ENSEMBLE RECORDINGS

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Aims

Prefrontal cortex (PFC) has a role in the higher nervous functions, such as attention, memory, executive processing and thought. Here we tackle the problem of decoding various parameters from the discharges of PFC neurons by applying different neural network architectures. Two monkeys attended to a rotating target on a screen while remembering a different, unmarked location.

Methods

We apply linear models, different fully-connected and convolutional neural network architectures to multichannel recordings from the electrodes in PFC in order to predict the attended and remembered locations of the moving target. Then we analyze the activity the neurons using neural net interpretability techniques to find patterns and reactions which depend on the target object position and movement direction.

Results

We succeeded in simultaneously predicting both the attended and remembered locations. The predictions by artificial neural networks by far exceeded the performance of a linear model applied to the same data. Moreover, the analysis of activity patterns exhibited by the neurons of artificial network shed light on how PFC activity could be processed in the brain.

Conclusions

We discuss the implications of these findings for brain-computer interfaces that strive to extract thoughts from PFC activity.

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ASSESSMENT OF OPENING OF THE BLOOD-BRAIN BARRIER BASED ON CROSS-RECURRENCE ANALYSIS

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Introduction

The blood–brain barrier (BBB) is a highly selective border protecting the central nervous system (CNS) from the penetration of microorganisms and toxins from the blood [1]. There is increasing recognition of the importance of BBB disruption in aging, dementia, multiple sclerosis, Alzheimer's disease, stroke, brain trauma, infection and tumors [2]. Normally, this mechanism plays a protective function. However, in some cases, the opening of the BBB may have important therapy value. For example, in the treatment of brain tumors, the possibility of injecting drugs from the blood into its tissues is of vital importance. In this case, the BBB was artificially opened using specialized drugs. However, such drugs have their own toxic effect and a number of side effects, and their use is possible only for health reasons. Recently, the possibility of a controlled opening of the BBB by sound stimulation [3] and laser radiation [4] has been shown. There is also evidence that the BBB can spontaneously open for a short time in some stages of sleep. However, the methods of express detection of the moments of BBB opening are still unknown. The availability of such methods can help to make a breakthrough in the field of personalized controlled therapeutic effects on a wide range of patients: those taking nootropic drugs, the absorption efficiency of which is extremely low in the closed BBB, patients suffering from brain cancer, patients prone to neurodegenerative diseases and those who have suffered strokes.

In this study on healthy rats, we developed method of diagnosis of opening the BBB using the non-linear analysis of the EEG activity with cross-recurrence analysis (CRA).

Methods

The experiments were performed on the same rats during two consecutive days: at the first day, EEG was recorded in awake state and during sleep and at the second day, EEG was recorded during the opening of the BBB in awake animals.

To analyze EEG signals we used CRA. It is a method for the analysis of dynamics of complex systems [5], which also shows good results when applied to the study of heart rate variability [6]. CRA is based on the projection of phase portraits of two signals into the same phase space, and the construction of time-domain structures in the form of horizontal and vertical segments, which characterize the proximity of the phase trajectories with a specified degree of accuracy. These structures were named cross-recurrence plots (CRPs). First, the EEG signals were filtered using a band-pass filter for extracting the oscillations in the δ-range [0-4 Hz] and θ-range [4-10 Hz]. Then, the phase space was reconstructed. In accordance with Takens recommendations, we used the delay method and reconstructed the phase space. For each state, the CRPs are qualitatively different. However, no quantitative information can be obtained from visual analysis of the CRPs. Therefore, we also calculated a number of well-established numerical indices from the CRPs. All calculations were performed in accordance with [7].

Results

The results of the CRA indices show that characteristics of the δ-range oscillations of the brain activity are most similar in the awake state with the opened BBB and during the normal sleep, and the both these states drastically differ from the awake state with the closed BBB. It is most interesting that these dynamics, which occurs both during the normal sleep and after activation of brain fluids drainage (caused by the opening of BBB) is developing in the δ-range, which is associated with deep sleep.

Conclusions

The dynamics of the δ−range oscillations in the rat EEG signals qualitatively changes after the opening of BBB. In this state it becomes similar to the electrical brain activity during the normal sleep. The obtained results

illustrate that activation of the brain fluid drainage system is the main cause of changes in the characteristics of the δ−range oscillations in the rat EEG signals when transitioning between the normal sleep, wakefulness, or the open BBB states.

Acknowledgements

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REAL TIME METHOD OF AUTONOMIC CONTROL LOOPS SYNCHRONIZATION DIAGNOSTICS

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Abstract

The analysis of non-stationary signals is an important problem of nonlinear dynamics [1]. However, the analysis of the time series of complex objects requires the development of specialized methods [2]. Objects of biological nature, in particular, elements of the human cardiovascular system (CCC), are important examples of such systems. The purpose of the work is to develop a method for diagnosing phase synchronization of autonomic blood circulation control loops in real time.

Methods

In [3], a method was proposed for diagnosing phase synchronization areas based on signals from the cardiovascular system. The method was based on the estimation of the slope of the approximating direct signal of the instantaneous phase difference $\Delta\varphi(t)$ in sliding windows over the width b_α. An interval is diagnosed as a phase synchronization section if its duration is more than l_α and $|\alpha_i| \le |\alpha_0|$, where α_0 is a threshold value. The method has a number of disadvantages, including the inability to a priori estimate the values of free parameters, quadratic complexity, and the use of floating-point arithmetic in calculations.

The proposed approach develops the ideas proposed in [4]. The method is based on averaging the values of the instantaneous phase difference $\Delta\varphi(t)$ in sliding windows of width w. Let φ_i be the average value for the i-th window. The interval T_j is diagnosed as the phase synchronization interval if $\triangle\varphi_i = |\varphi_i - \varphi_{i-1}| \ge \varphi$, $\forall i \in T_j$ and $T_j > T_s$, where ϕ is the threshold value, T_s is the minimal length of the synchronous interval. The lengths of asynchronous intervals must be less than T_n. The parameters of the new method can be estimated from a priori considerations about the data.

Results

To adjust and verify the compared methods, we used a model for generating test instantaneous phase differences $\Delta\varphi(t)$, similar to [5]. Having a priori information about the position of the synchronization intervals, ROC curves were plotted (Fig. 1). At the point where the ROC curve is cut by the diagonal, the proposed method demonstrates the values TPR = 0.837, FPR = 0.163, and the well-known method TPR = 0.842, FPR = 0.158. AUC (Area Under the Curve) for the known method is 0.911, and for the proposed one - 0.910. As you can see, the developed method demonstrates accuracy close to the known method.

To compare the computational complexity of the two methods, the execution time was estimated from the length of the implementation. With a row length of 5000000 points, the known method calculated within 76742.2 ms, and the proposed one - 312.2 (time ratio 245.8).

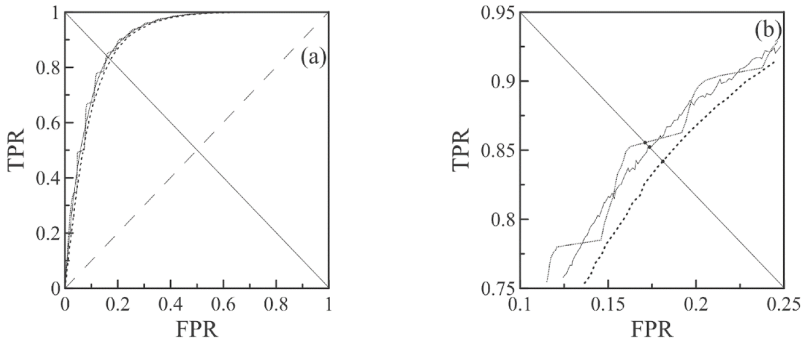

Fig. 1. Results of the comparison of methods in the course of analysis of test data that reproduce the statistical properties of signals of biological nature: (a) ROC-curves constructed during enumeration of method parameters, (b) - an enlarged fragment in the area of the ROC-curves section by the diagonal. Thin line proposed method, dotted line known method based on the approximation of the phase difference, dash and dash line known real-time analysis method.

Conclusions

A method for diagnosing phase synchronization of autonomic blood circulation control loops in real time is proposed. The method shows close accuracy to the known method based on the approximation of the instantaneous phase difference in a sliding window. At the same time, the proposed method demonstrates performance more than 200 times higher than the performance of the known approach. Also, the algorithm that implements the method includes only the simplest operations of addition and comparison, which makes it possible to effectively use it in wearable real-time devices.

Acknowledgements

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SYNCHRONIZATION IN THE NEURON-ASTROCYTE NETWORK

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The investigating of synchronization effects in the dynamics of systems consisting of interacting biological oscillators is one of the most advanced areas of modern radiophysics. A striking example of such systems is networks consisting of interacting brain cells: neurons and astrocytes. Neurons that can generate electrical impulses are considered the main signal cells of the brain. More recently, it was discovered that astrocytes are also able to generate calcium pulses in response to the passage of impulse signals through the neural network. It is believed that calcium impulses in astrocytes are involved in the biophysical mechanisms of bidirectional interaction between neurons and astrocytes. Having their own non-trivial dynamics, neural and calcium oscillators form networks with complex intercellular interactions. This work is devoted to the study of nonlinear effects of collective dynamics of neuron-astrocyte networks, such as synchronization, formation of activity structures, regularization and chaotic oscillations. It is believed that these phenomena are the basis of various processes of information processing in the brain, for example, learning and memory, understanding the mechanisms of which is one of the priority and urgent tasks of modern radiophysics. Understanding the mechanisms of astrocytic regulation of neural activity opens up a number of potential opportunities for indirect therapeutic effects on the brain's neural networks.

The influence of astrocytes on the signal transmission processes in the neural network is the aim of paper studies. The architecture of the neuron-astrocyte network in the form of interacting three rings, corresponding to experimental data on the organization of networks in the brain, was considered. The first ring of the system is an ensemble of excitatory neurons, each of which is stimulated by an uncorrelated Poisson process that simulates the effect of an external neural network. The second ring of the system is a network of inhibitory neurons that receive signals from excitatory neurons, and which are under the influence of astrocytes that form the third ring of the network under consideration. The generation of calcium impulses in astrocytes is induced by the activity of the first ring of the system. The effect of astrocytes is to a change in the amplitudes of the action of excitatory neurons on inhibitory ones, as well as to a change in the effective forces of connections in the second ring. The paper examines the collective dynamics of signaling of inhibitory neurons. The dynamics of the neuron-astrocyte interaction in the unit cell of the considered network consisting of two neurons and two astrocytes was studied earlier [1].

The Hodgkin-Huxley model [3] with the Mainen modification [4] was chosen as a description of the dynamics of the membrane potential of a neuron. Unidirectional pulse communication between neurons simulates the dynamics of a chemical synapse [1]. The dynamics of intracellular calcium concentration in astrocytes is described by the Ullah-Jung model [2]. The effect of astrocytes on neurons was modeled using the previously proposed approach [1]. When the calcium concentration reached the threshold, astrocytic regulation of synaptic transmission in the network of inhibitory neurons was activated. The experimentally confirmed effects of astrocyte-mediated amplification and suppression of the synaptic connection strength in the neural network were considered.

To study the effect of astrocytic regulation of signal transmission on the correlation of neural network signaling, the synchronization coefficient and the average generation frequency were calculated for the time series of membrane potentials of inhibitory neurons. The network-wide synchronization coefficient was calculated as the average value of the synchronization coefficients for each pair of neurons in the network in a time window of 500 ms. The regions of the model parameters corresponding to the synchronization in the neural network were calculated.

In this work, it is shown that the astrocytic regulation of signal transmission between neurons affects the establishment of synchronization of the activity of the neural ensemble at the times of calcium dynamics in astrocytes. It was found that the influence of astrocytes can lead both to the expansion of the synchronization region and to the displacement of its boundaries.

Acknowledgements

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DYNAMICS OF RATE AND SPIKING NEURAL NETWORKS FOR MODELING COGNITIVE TASKS

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The aim of this work is to contribute to the methodology of constructing recurrent artificial neural networks that simulate the functional properties of brain networks. The trained neural networks consist of rate or spiking units and are studied by means of approaches of nonlinear dynamics and complex networks theory in order to unravel dynamic and structure mechanisms of performing particular functions.

Design of a model usually includes the following stages. First, a neurobiological phenomenon is formulated as an objective function that transforms input stimuli into output stimuli in a certain way. Second, a basic artificial neural network is initialized. Third, the network is trained after which the model is able to generate output responses based on input stimuli in a manner that is qualitatively or even quantitatively similar to the real system. The trained network is a dynamical system that can be studied by methods of nonlinear dynamics, and one can find the population mechanisms of the performed function of translating input signals into output responses.

We design several types of rate and spiking neural networks to perform target functions inspired by cognitive neuroscience. One of prototype experimental examples is the perception of vibrotactile stimuli presented to a monkey with a delay, their comparison and the animal's motor response about which of them is larger. Based on machine learning techniques, we build model systems and analyze the dynamic mechanisms underlying their work. It has been found that after supervised training, artificial neural networks are able to perform target functions similar to experimental prototypes, while the dynamic properties of model neurons are qualitatively similar to those found in the experiment, in particular, they are characterized by the phenomenon of mixed selectivity. In addition, in the artificial neural network, the so-called demixed principal components were identified which are the building blocks of the full multidimensional activity. These components relate the neuron dynamics with individual parameters of the task being performed.

Acknowledgements

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BRAIN-COMPUTER INTERFACE FOR OLFACTION: ACCOUNTING FOR RESPIRATION AND DECODING ODORS FROM EEG

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Aims

The final aim of our research is to develop a brain-computer interface (BCI) for olfaction. Our research program relies on modern olfactory displays and advanced processing of respiratory data in order to develop methods for robust olfactory BCI systems. Here we present the initial results from 17 subjects of our ongoing study. We observe that aligning EEG records to respiration cycle provides significant improvement to data analysis and allows to observe EEG modulations related to odor processing. EEG classification for different olfactory stimuli is the first step in this research, followed by the development of odor-imagery BCIs and odor-based neurofeedback.

Methods

We designed an experimental setup where subjects are involved in an olfactory discrimination task. Olfactory stimulus delivery is conducted with the use of a modern olfactory display while electroencephalographic (EEG) and respiration data are collected. Seventeen right-handed healthy volunteers (N=17, females=7, males=10, median age = 31, SE=7.7). Perceived odors delivered with a special olfactory display developed by the Sensory lab, Inc. This display uses piezoelectric transducers to evaporate liquid odorants. Subjects sat in a room with a constant top-down air flow. Moreover, this setup enables rapid (with a ~500ms latency) onset and offset of olfactory stimuli.

Experiment setup

Four liquid stimuli were used: vanilla, coffee, citrus and odorless water. Participants reported odor type with two-dimensional joystick movements. The joystick was placed under the right hand of the participant. Subjects started each trial by pressing a button with the left hand, which allowed data syncing the different recording devices. EEG data were collected with a Smart BCI system. 19 electrodes were positioned on the scalp according to the International 10–20 system with A1+A2 ears reference. Respiration data were collected with KARDi2-NP polygraph amplifier and TRSens temperature sensor for nasal-oral breathing.

Experimental task

The task is an instructed-delay task that required a sensorimotor transformation of an odor into a pointing movement with the joystick. Each odor (including no-smell condition) was associated with a visual object: a square, circle, triangle, or a star. Odor-object pairs were randomly generated for each participant and remained constant during each trial.

Following the training (40 trials, 10 x odor, random order), an odor discrimination session was run (80 trials, 20 x odor, random order). Participants were instructed to hold their breath until fixation cross turned green. Odor

delivery started immediately after the button was pressed. Following a 2-s delay, the fixation cross changed color from red to green and the participant made the first inhale. After the subject perceived the odor for the other 10s, 4 objects appeared on the screen (at 0, 90, 180, and 270° positions); one of them represented the correct response. With this design, EEG and respiratory data were collected during 3 delay intervals: (1) no odor, (2) odor discrimination withot any motor preparation, and (3) motor preparation; and a peri-movement interval. After the experiment participants were asked to name the odors perceived during the experiment.

Respiratory data processing

All participants we instructed to start breathing when the fixation cross turned green. An algorithm was developed to detect the moment when subject started to inhale and feel the olfactory stimulus. The algorithm utilized a a sliding window, and the inhalation start was determined as the curve deviation from a stationary value.

Results

All participants correctly identified odorless water and majority of them (10 out of 17) could identify coffee. Yet, only 5 and 3 subjects could correctly name citrus and vanilla odors at their concentration offered by the Sensory lab. Nontheless the subjects performed well in the discrimination task with mean success rate of 93.8% (SD=14,5%). Moreover, we found a clear EEG modulation pattern associated with the inhalation onset, which often consisted of an enhancement of ~8-10 Hz rhythmic activity. This EEG modulation was odor-dependent.

Discussion

Although olfaction is phylogenetically an old system present in many living organisms, it receives relatively little attention in BCI studies. Here we developed an experimental setup that incorporates both the measurements of respiratory cycle and controlled delivery of olfactory stimuli. We found that EEG patterns depend on the respiration phase and odor properties. As such, our approach could generate multiple research and clinical applications, where neural representations of odors are decoded and used for early diagnostics of neurological disorders known to be connected to the altered sensation of smell; and for BCI where orders are used to therapeutically influence brain activity (including odorant delivery during sleep).

RECONSTRUCTION OF NODES AND COUPLINGS IN THE NETWORK OF NEURONAL OSCILLATORS

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The aim of our study is the reconstruction of model equations for the network of 3rd order neuron-like oscillators [1] from time series. The nodes of the network are able to exhibit different dynamical regimes including quasiharmonic oscillations, spiking, bursting, and chaotic behavior. We consider an ensemble of oscillators described by the system of the following differential equations:

$$\begin{aligned} \dot{\varphi}_i &= y_i, \\ \dot{y}_i &= z_i, \\ \varepsilon_{i,1}\varepsilon_{i,2}\dot{z}_i &= \gamma_i - (\varepsilon_{i,1}+\varepsilon_{i,2})z_i - f_i(\varphi_i)y_i + \sum_{j=1, j\neq i}^{D} k_{i,j}(y_j - \end{aligned} \qquad 1)$$

where the variables ϕ_i and y_i are the instantaneous phase difference and the corresponding frequency difference between a tunable oscillator and a master oscillator, respectively, z_i is the velocity of changing of the

phase difference y_i, the parameters γ_i define an initial frequency detuning, $\varepsilon_{i,1}$ and $\varepsilon_{i,2}$ are the parameters of control loop, and $k_{i,j}$ are coupling coefficients, $f_i(\varphi_i) = (1 + \varepsilon_{i,1} \cos \varphi_i)$ are nonlinear functions, D=10 is the number of oscillators.

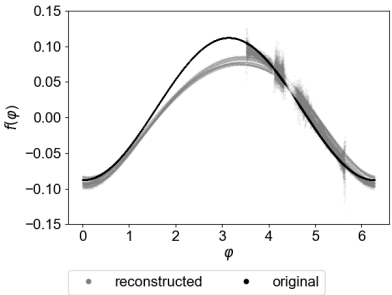

Fig.1. Reconstructed nonlinear function of a neuron in bursting regime with added 1% noise

Different coupling architectures including chain, ring, star, and random architecture were considered. For three coupling architectures: chain, ring, and random couplings, all non-zero couplings were set the same and equal to k=0.01. For a star, the coupling coefficients characterizing the coupling from the central oscillator to the peripheral oscillators were equal to k=0.02, while the coupling coefficients characterizing the coupling in the opposite direction were equal to k=0.01.

In relation to neuron dynamics, the variable y_i can be interpreted as a variable describing a change in the membrane potential, the parameters $\varepsilon_{i,1}$ and $\varepsilon_{i,2}$ allow one to set the necessary dynamical regime, and γ_i are the parameter which has an effect similar to the external current in the Hodgkin-Huxley model.

Therefore, the reconstruction task is formulated further in the way, that only the variables y_i are observed. To reconstruct the complete state vector, the variables z_i are obtained with numerical differentiation using smoothing polynomial, constructed from m data points. Following the ideas of [2], we construct a target function by minimizing the length of a line connecting the points of reconstructed nonlinear function f_i for each oscillator. The reconstructed nonlinear function of one oscillator is presented in Fig.1. The proposed algorithm allows to reconstruct not only parameters of individual oscillator, but also coupling coefficients and reveal the coupling architecture. The results of the coupling architecture reconstruction are presented in Fig.2. Black squares correspond to the detected existing couplings. The numbers of driving neurooscillators are shown on the horizontal axis, while the numbers of driven oscillators are shown on the vertical axis

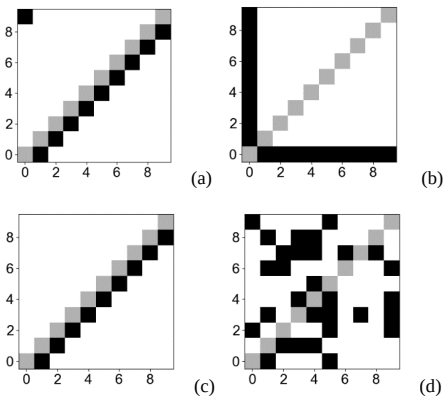

Fig.2. Reconstruction of coupling architecture for the ring (a), star (b), chain (c), and random couplings (d) in spiking regime of oscillations

Thus, we reconstructed for the first time a network of 3rd order systems with both unknown coupling architecture and unknown nonlinear function of each node using only scalar time series of individual nodes.

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FITZHUGH–NAGUMO OSCILLATORS ON COMPLEX NETWORKS MIMIC EPILEPTIC-SEIZURE-RELATED SYNCHRONIZATION PHENOMENA

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We study patterns of partial synchronization in a network of FitzHugh–Nagumo oscillators with empirical structural connectivity measured in human subjects [1]. We report the spontaneous occurrence of synchronization phenomena that closely resemble the ones seen during epileptic seizures in humans. In order to obtain deeper insights into the interplay between dynamics and network topology, we perform long-term simulations of oscillatory dynamics on different paradigmatic network structures: random networks, regular nonlocally coupled ring networks, ring networks with fractal connectivities, and small-world networks with various rewiring probability. Among these networks, a small-world network with intermediate rewiring probability best mimics the findings achieved with the simulations using the empirical structural connectivity. For the other network topologies, either no spontaneously occurring epileptic-seizure-related synchronization phenomena can be observed in the simulated dynamics, or the overall degree of synchronization remains high throughout the simulation. This indicates that a topology with some balance between regularity and randomness favors the self-initiation and self-termination of episodes of seizure-like strong synchronization.

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EXTREME EVENTS IN SMALL ENSEMBLE OF BURSTING NEURONS WITH CHEMICAL AND ELECTRICAL SYNAPTIC COUPLINGS

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Extreme events (EEs) are rare non-periodic large amplitude deviations of the observable variable from its typical range of values when changing the control parameter of the system. One of the striking examples of EE in neuroscience and medicine are epileptic seizures [1]. From the mathematical point of the view, in order to reproduce EEs one can use a class of dynamical systems, in which the phase point spends most of the time close to a specific chaotic attractor, but at certain rare time intervals it moves to distant regions of the phase space. In [2] a statistical criterion for EEs was introduced, according to which an event is classified as EE if its amplitude exceeds the critical level Hs =μ-6σ, where μ is mean value and σ is standard deviation.

Our aim is to study the influence of additional electrical coupling on extreme events and chaotic dynamics observed in the minimal ensemble of two bursting Hindmarsh-Rose neurons with mutual chemical synaptic couplings, which is described by the following equations:

$$\begin{aligned} \dot{x}_i &= y_i+bi2-ai3-z_i+I-k_i(x_i-vs)\Gamma(x_j)+k(x_j-x_i) \\ \dot{y}_i &= c-dx_i2-y_i \\ \dot{z}_i &= r[s(x_i-xR)-z_i] \\ i, j &= 1, 2\ (i\neq j) \end{aligned} \qquad 1)$$

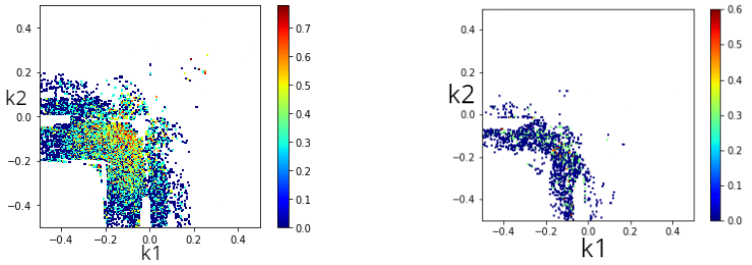
where x_i describes the membrane potential of the i-th neuron, the variables y_i and z_i correspond to fast and slow ion currents flowing through the membrane of the i-th neuron. The parameter $r \ll 1$ determines the ratio of the characteristics time scales of these currents, r=0.001. The parameter I describes the external current applied to the neuron. In our study I=4. Other parameters describe the nonlinearity of the membrane conductance: a=1, b=3, c=1, d=5, xR=-1.6, s=5, which are typical values for bursting regime in an isolated element.

Chemical synaptic couplings are described by term $k_i(x_i-vs)\Gamma(x_j)$ where

$$\Gamma(x)=1/(1+\exp(-\lambda(x-\Theta)))$$

is a sigmoid function with parameters =10, Θ=-0.25. Parameters k1, 2 correspond to the strength of chemical couplings and are control parameters of the system. Depending on its values, one can simulate different types of the impact: inhibitory (k1, 2<0), excitatory (k1, 2>0) and mixed one (k1>0 and k2>0 or vice versa). The electrical synaptic coupling between elements is described by the term k(xj-xi) where parameter k is responsible for the strength of this coupling.

In [3] a case of purely chemical interactions (k=0) was studied. The existence of EEs for time series of the variable xII=x1+x2 was shown for a wide range of parameters k1,2. On the basis of these results, in the presented study the influence of electrical coupling (k≠0) on the dynamics of system (1) was investigated using numerical methods of nonlinear dynamics and statistics. In particular, it was shown that the addition of a weak electrical coupling (see Fig. 1) leads to shrinking of the regions of stability of EEs and the emergence of regular neuron-like activity.



(a) (b)

Fig. 1. Maps of EEs on the plane (k1,k2) for different fixed values of k. Colored region denotes EEs that cross the Hs line. A range of colors indicates a number of events counted in a color bar in a log scale. (a) k=0, (b) k=0.1

It was proved that the presence of EEs in the system (1) is connected to phenomenon of hyperchaos. Increase in the strength of electrical coupling up to a certain threshold value leads to the destruction of hyperchaotic regimes (characterized by two positive Lyapunov exponents), which, firstly, become chaotic ones (with one positive Lyapunov exponent) and, secondly, transform into regular bursting activity. Nevertheless, chaotic temporal patterns appear again for a certain range of values of k, but in this case it cannot cause EEs and disappear with further increase in the strength of the electrical coupling.

Acknowledgements

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INTERACTION OF AUTONOMIC CONTROL LOOPS OF BLOOD CIRCULATION IN PATIENTS WITH COVID-19

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Introduction

This work aims to study the features of autonomic regulation of the heart and blood vessels in patients of different ages with a confirmed diagnosis of Covid-19.

Several published works have provided data on the effect of SARS-CoV and SARS-CoV-2 viruses on the state of autonomic nervous regulation of the cardiovascular system. Depending on the severity of the disease, the degree of damage to internal organs and related problems, this is associated with the stimulation of the secretion

of the Angiotensin-converting enzyme 2 (ACE2), which is the entry point for coronaviruses [1-2]; depletion of the resources of the sympathetic regulation system due to cytokine release syndrome with extreme macrophage activation and a significant increase in inflammatory cytokines, which in turn balanced by a compensatory anti-inflammatory response and modulated mainly by the anti-inflammatory cholinergic pathway and the parasympathetic nervous system [3]; with damage to the myocardium and nerve fibres innervating the heart and blood vessels [4]; with the invasion of the virus into the lowest region of the brainstem that controls several autonomic activities, including the heart and breathing [5].

Material and methods

In this work, we obtained some experimental signals of electrocardiogram and photoplethysmograms of blood vessels from patients with Covid-19 aged 25 to 68 years and healthy subjects of the corresponding age group. A standard certified polyrecorder EEGA-21/26 “Encephalan-131-03” (Medikom MTD Ltd, Taganrog, Russia) recorded the signals. The sampling frequency was 250 Hz, the filtering bandwidth was 0.016-250 Hz for the maximum possible low-frequency transmission. The electrocardiogram was registered in 1 standard lead, according to Einthoven. The sensor for recording the photoplethysmogram was provided with an infrared emitter and was located on the ring finger of the subjects [6-7].

In this work, the main tools were the methods of spectral analysis (construction of spectra using the Welch method, cross-spectral analysis) and phase dynamics analysis (calculation of the coherence coefficient and the previously proposed estimate of the total percentage of phase synchronization) [8-13].

Results

The creation of the coherence function (cross-spectral analysis) between the signals of the RR-intervals and the vascular photoplethysmogram made it possible to reveal the difference between the studied samples. Also, the research showed signs of the influence of age on the connectivity of the studied loops in the sample of healthy people.

Assessment of the phase synchronization of the processes of nervous regulation of heart rate and vascular tone did not reveal significant differences between patients and healthy subjects.

Conclusion

Thus, the spectral analysis methods made it possible to determine the features of the nervous regulation of the cardiovascular system in patients with Covid-19. At the same time, a weakening of the connection between processes in the low-frequency loops in healthy subjects with age was also revealed.

Acknowledgements

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THE RAPID DYNAMICS OF CA1 HIPPOCAMPAL PLACE CODE FORMATION IN A NOVEL ENVIRONMENT

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Aims

Hippocampal place cells are an object of highlighted interest in neuroscience. Their place-specific firing patterns (place fields) constitute so-called cognitive maps which can retain for days [1,2], but also can be remapped in environment-dependent manner. However, the principles driving the formation of the cognitive map in a novel environment remain unclear. Here we focus on the first moments of the exploration of a completely novel context, and define a critical time for cognitive map tuning by means of miniscopic neuronal recordings.

Methods

Twelve male C57BL6 mice aged at least 2 months were taken for this study. Mice underwent two surgical stereotaxic operations under anesthesia: first, viral vector particles coding various fluorescent calcium indicators (GCaMP6, NCAMP7) under CAG promoter were injected to the field CA1 of the hippocampus. Then, after 2weeks recovery, mice were subjected to GRIN-lens implantation above the microinjection site. After another 2 weeks mice were checked for a fluorescent calcium signal and baseplates for NVista HD miniscope were mounted on the scull surface. Finally, awake mice with attached NVista HD miniscopes were put into a novel environment: circular O-shaped track with visual cues on surrounding curtains. Mice spent 15 min exploring the track while neuronal calcium signal and behavior video tracking were captured. Locations and traces of neurons were extracted from neuronal video data with MIN1PIPE routine and then place fields were detected by means of surface approximation in angle-time domain. For each place field a tuning time was defined post hoc as amount of time spent before a correspondent place cell begin repeatedly fire in the field.

Results

Most of animals demonstrated rapidly tuned cognitive maps with uniform distribution of place fields, covering all sectors of the track. Spatial selectivity of the cognitive map was shown by means of dimensionality reduction methods: the in-track locations of animals were successfully decoded from neural activity. Place fields showed average tuning time around 140 seconds. More than 30% place cells get tuned within the first in-track lap, while more 60% place cells do it within the first 3 laps along the track.

Conclusions

Taken together, these results suggest that cognitive maps form uniformly and rapidly not only in time domain, but also in spatial domain. This can provide a background for the searching for early behavior or intrinsic triggers for a cognitive map formation.

Acknowledgements

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MULTIPLEX HETEROGENEOUS NETWORKS OF HODGKIN-HUXLEY-TYPE OF MODELS WITH BISTABILITY BETWEEN SILENT STATE AND BURSTING ATTRACTOR

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Networks of interacting oscillators are one of the most important research objects of the dynamics of complex systems in various fields of science. One of the most interesting areas is the study of the interaction of models of neurons described by the Hodgkin-Huxley formalism, since it is directly related to the study of the interaction of biological cells, and is also important for the development of artificial intelligence and machine learning [1].

Typical behavior corresponding to the normal mode of cell functioning described by the Hodgkin-Huxley formalism, such as neurons, pancreatic beta cells, cardiomyocytes, and others, is a dynamic mode corresponding to the bursting attractor. Bistability can be observed in such systems. Moreover, different types of attractors can coexist, various types of multistability are discussed in the paper [2]. One of the most interesting options is the multistability between a bursting attractor and a stable equilibrium state. In [3], a modification of the well-known Sherman model is proposed, in which, in addition to a typical bursting attractor, an equilibrium state is stabilized. The modification of the model consists in taking into account an additional ion channel with a non-monotonic characteristic, which locally changes the nullcline of the model's fast manifold, i.e. the model retains all of its basic properties. A new ion channel can be interpreted as a defect in cell communication, since the probability of its opening is lower than that of a conventional channel. The presence of similar models makes it possible to model heterogeneous networks, some of the elements of which have a communication defect, and some do not. From the point of view of dynamical systems, such a situation will correspond to the fact that some of the elements of the network will demonstrate only a burst attractor, while the equilibrium state will be unstable. And some of them will also mainly demonstrate bursting oscillations, while a stable state of equilibrium with a small basin of attraction will coexist with them. The study of the dynamics of a heterogeneous network of interacting models showed [4] that with a ratio of elements with and without pathology in a ratio of 1:1, the state of equilibrium will be unstable and pathology will not appear in the system. With an increase in the number of pathological elements (with bistability), the equilibrium state can be stabilized, however, the stabilization threshold for the coupling strength parameter increases with a decrease in the ratio of normal elements to elements with pathology, which indicates the presence of resistive properties in such systems and preservation of the normal mode of cell functioning.

The **aim** of the present work is to simulate a heterogeneous multiplex network to determine the opportunity to exhibit atypical behavior. We will assume that abnormal elements (with bistability) may behave more actively than normal ones. In the context of such an assumption, the ratio of defective and non defective elements can change to manifest pathological behavior. In Fig.1a schematic representation of minimal multiplex heterogeneous network is presented. Purple nodes correspond to models with unstable equilibrium and burst attractor, red nodes manifest coexistence between stable equilibrium and burst attractor.

As the **main tool** we used numerical methods for solving ordinary differential equations and software package for numerical bifurcation analysis XPPAUT.

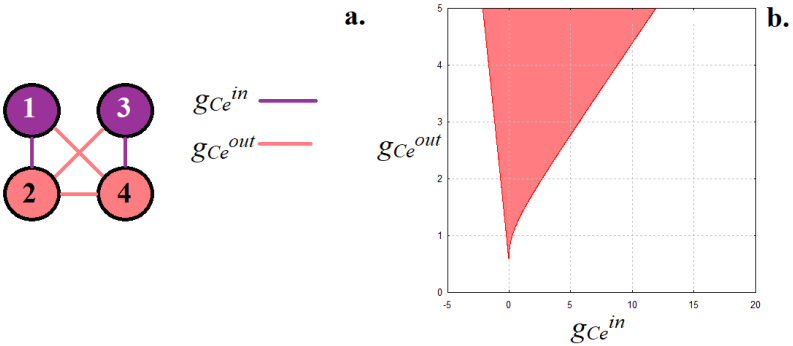

Fig.1. **a.** Schematic representation of minimal multiplex heterogeneous network, **b.** bifurcation diagram determined area of stable equilibrium.

Results

An analysis of the stability of the equilibrium state was carried out using the XPPAUT software package depending on the coupling coefficients. Figure 1b shows the bifurcation diagram for minimal network model; the area where the equilibrium state is stable is marked in pink. The abscissa shows the parameter responsible for the strength of communication within the subnetwork, and the ordinate shows the parameter responsible for the communication between subnets, implemented by elements with pathology. Figure 2b clearly shows that the area of equilibrium stabilization has a threshold in terms of the parameter of communication between subnets, for $g_{Ce}^{in} = 0$, the strength of communication between subnets is required to stabilize the equilibrium. With an increase in communication within the subnets, the stabilization threshold increases. Thus, the interaction within the subsystems interferes with stabilization and stronger interaction between the subnets is required for stabilization. In a heterogeneous globally coupled network only unstable equilibrium will be observed. More active behavior of elements with pathology can contribute to the occurrence of pathological conditions in a network with the same number of elements with and without pathology. If the pathological element is replaced with a normal one in one of the subnets, the equilibrium state will destabilize. Thus, for a model of 4 cells, at least 50% of elements with pathology are required for it to manifest itself in the entire network. In the work we present results for larger networks with different topologies.

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MODELING EPILEPTIC SEIZURE INITIATION BY MEANS OF MESOSCALE ENSEMBLES OF NEUROOSCILLATORS

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This work aims to provide simple network oscillatory models of two types of epileptic activity: spike-wave discharges (SWDs, the primary manifestation of absence seizures) and limbic discharges corresponding to convulsive temporal lobe seizures. When models based on oscillatory ensembles are considered, the epilepsy is often treated as a result of hyper-synchronization of large brain areas. This matches the general and common idea that epilepsy is a network phenomenon. However, according to the modern International league against epilepsy (ILAE) classification [1], different epilepsy types have not only different clinical and electroencephalographic manifestations, but also are developing very differently, having unequal mechanisms of main rhythm generation. Here we show that relatively simple, but very different types of dynamical activity can be considered as mathematical models of epileptic activity matching existing neurophysiological knowledge.

Methods and models

One of the main problems in the study of absence seizures is that the mechanisms of SWD termination are not still revealed [2,3], stating that seizures are stopping “by themselves”. From the point of view of the nonlinear dynamics the possible explanation of such a phenomenon is to consider SWDs as a long transient process rather than a regime on an attractor. This transient can originate due to different reasons including external input from some peripheral areas [4]. In this work we propose the small model of 14 neurons (actually nodes, corresponding to larger groups of similar cells) of four types: 4 cortical pyramids, 4 talamocortical neurons, 4 reticular thalamic neurons, one interneuron and one trigeminal neuron. All neurons except the tigeminal one, which is connected to the remaining netwok only for a shot time, are in the nonoscillatory mode. Since the absence seizures are primary generalized ones [1], the main oscillation rhythm and oscillation shape originate from the whole network organization rather than from the properties of a single neuron or some group of neurons.

The limbic seizures are considered as focal seizures [1] with focal area located somewhere in the hippocampus [5]. However, the modern investigations show the focus to be a circuit distributed in a wide area rather than an small localized spot [6]. Since the limbic seizures are long, vary a lot even for a single patient and very nonstationary, the circuit/scheme is necessary which can be simply rearranged in the brain to generate the main rhythm. Then, the mechanism of such an activity spreading to the entire hippocampus is necessary. We propose a unidirectional ring of neurons generating the main rhythms as a results of delayed coupling, with all of them being in under threshold (nonoscillatory) regime by itself. Two additional subnetwork are also implemented. One small subnetwork is necessary to initiate the activity in the main ring. The other one larger subnetwork models the surrounding areas and is synchronized by the main ring due to some event, e.g. coupling rearrangement in case of memorizing new information (long time memory is one of the primary tasks of hippocampus).

Results

When modeling SWDs three different types of equations were used for the single cell description: FitzHugh-Nagumo, Morris-Lecar and Hodgkin-Huxley equations. Two types of coupling were tested: linear coupling and sigmoid one. A complete class of 88 coupling matrices providing models with similar but different in detail network organization were tested with different initial phase of external driving. The long regular transients (up to 20-200 oscillations depending on the model and coupling type) were found for many of these 88

matrices for all types of node equations and both connection types. This validates the proposed hypothesis that SWDs can be described as long transients in response to short in time external driving, with these transients being possible due to special organization of connectivity matrix.

Using two types of models for a single neuron: simple FitzHugh-Nagumo oscillators and extended Hodgkin-Huxley equations and two types of coupling: simple linear coupling and synaptic sigmoid one, we have shown not only that one can induce the stable oscillations in unidirectional coupled ring of model neurons, but also that one can control the oscillation period both by changing the coupling delay and the number of cells in the ring. We also have shown the possibility to synchronize the outer larger network, which is the first step of seizure generalization.

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SHORT-TERM MEMORY IN MODEL OF NEURAL NETWORK ACCOMPANIED BY ASTROCYTES

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Aims

Recent experimental and theoretical studies [1] have shown that the astrocyte can act as a temporal and spatial integrator, determining the level of spatio-temporal coherence in the activity of the accompanying neural network. In particular, such spatio-temporal integration, based on fast and local events of activation of small compartments along the astrocytic processes, leads to long-term astrocyte-mediated changes in the synaptic functionality of the neural network. Astrocyte activation is usually understood as an increase in intracellular calcium concentration. It has been shown that calcium impulses in astrocytes are involved in biophysical mechanisms of bidirectional interactions between neurons and astrocytes. The calcium signal leads to the release from the astrocyte of neuroactive substances that change the efficiency of synaptic transmission. Thus, activation of the astrocyte can induce spatial synchronization in neural ensembles determined by the morphological territory of the astrocyte. Consequently, the phenomenon of short-term working memory can be realized in the

neuron-astrocytic network, due to the effect of astrocytic modulation of synaptic transmission in the neural network.

Methods

The developed model of the neuron-astrocyte network consists of three layers. The first layer consists of excitatory neurons, the second - of inhibitory neurons, the third - of astrocytes. The dynamics of the membrane potential of each neuron in the network is described by the Izhikevich model [2]. The neurons of the first layer are interconnected by local excitatory synaptic connections. Moreover, neurons in the first layer can activate inhibitory neurons in the second layer. In turn, the neurons of the second layer are connected with the neurons of the first layer by inhibitory nonlocal synaptic connections. Excitatory connections within the first layer and inhibitory connections are trained according to the STDP rule [3].

Each astrocyte in the network is connected to neighboring astrocytes by gap junctions Cx43, which are permeable to molecules of inositol - 1,4,5-triphosphate (IP3) and calcium ions (Ca^{2+}). To simulate the dynamics of each astrocyte, we used the Li-Rinzel model [4].

Astrocytes interact with neuronal subnetworks (4x4 with overlap in one row) using chemicals that diffuse in the extracellular space. The connection between neurons and astrocytes is organized as follows: in the case of generation of an action potential on a presynaptic neuron, the concentration of a neurotransmitter (glutamate) in the corresponding synapse increases for a short time. With a sufficient level of synchronous activity of the neural ensemble interacting with this astrocyte, an IP3 dependent increase in the intracellular calcium concentration occurs in it. Achieving a certain threshold of calcium concentration in the astrocyte induces the release of the gliotransmitter from the astrocyte to synapses, which leads to a change in the efficiency of synaptic transmission in the ensemble of synapses interacting with this astrocyte.

Results

The proposed memory architecture ultimately demonstrated synergistic functionality in loading information and reading it by the neural network and storing it by astrocytes. In contradistinction to models of neural networks without an accompanying astrocytic network, in which memory is encoded in synaptic connections and their plasticity, which inevitably leads to an overlap problem, our model separates functionality using astrocytes as a repository of patterns. Even with significant overlap, they can be successfully retrieved due to astrocytic coherent synaptic modulations and synchronous neuronal activation that provide selectivity.

Conclusions

This model confirms the theoretical hypothesis that astrocytic modulation of synaptic transmission can participate in the functional formation of short-term working memory. We show that the NMDAR-mediated enhancement of excitatory synapses induced by D-serine released from astrocytes in the PFC may serve as a possible molecular mechanism of working memory.

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HIERARCHICAL NETWORKS WITH INTELLIGENT FUNCTIONS ON THE BASIS OF PULSE-COUPLED MICRO-OSCILLATORS

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Abstract

Hierarchical networks of pulse coupled micro-oscillators and excitable cells have been considered as a micro-robot with intelligent functions. These networks are capable of adapting to external signals and even making decisions. Our hierarchical networks consist of several functional blocks. (1) Block "Antenna" which responds on external pulse signals. These signals generate in Antenna one of the several possible attractors. The attractors are stable dynamic modes. (2) Block "Antenna Reader", which determines what dynamic mode originated in the Antenna. (3) Block "Central Pattern Generator" (CPG), which determines the inner dynamic state of the entire hierarchical network. This unit, like the Antenna, has several dynamic modes between which switching can occur, *i.e.*, multi-rhythmicity takes place. (4) Block "Reader CPG", which determines in what dynamic mode the CPG is at the current moment of time. (5) "Decision Making" (DM) block, which collects information from two Readers and decides whether to switch the CPG to a new mode corresponding to the new external signals. (6) Block "Executor" which communicates (or execute) the decision made in the DM block to the CPG block.

The biological principles of the operation of neural networks are taken into account and the laws of nonlinear dynamics are used when such hierarchical networks are constructing. As an example of biological principles, the problem of the simultaneous arrival of several excitatory pulses to an excitable cell in the absence of a synchronizing frequency is considered. The role of Readers as carriers of a symbolic language and a tool for predicting the future, depending on the decision made by the DM block, is considered. Actively used methods of switching from one attractor to another, as well as the controllability of the excitability thresholds of excitable cells can serve as examples for laws of nonlinear dynamics. Methods for transmitting a pulsed signal using chemical waves for both excitatory and inhibitory types of coupling are also examples of the use of the laws of nonlinear dynamics in a micro-robot being constructed.

In the experimental implementation of a chemical micro-robot, the Belousov-Zhabotinsky reaction in micro-volumes is used as chemical micro-oscillators, although other types of micro-oscillators can be used as well.

HARDWARE IMPLEMENTATION OF PULSE COUPLING FOR ELECTRONIC NEURON-LIKE GENERATOR CONNECTION

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Aims

The aim of this work is to study synchronization of two neuron-like generators based on phase-locked loop and to develop hardware pulse coupling device to implement connection of two electronic neurons.

Methods

The work is focused on studying of neuron-like generator dynamics. Neuron-like generator based on phase-locked loop with a band-pass filter demonstrates various dynamic modes (regular spiking, various bursting modes including chaotic) both in mathematical model and in hardware [1,2]. The mathematical model of the neuron-like generator has the form:

˙=y

y˙=z

12z˙=-1+2z- 1)

1+1cosφy+Isyn

where y can be interpreted as a variable describing the change in the membrane potential, parameters ε_1 and ε_2 make it possible to set a necessary dynamic mode, and γ has an effect that is close to that of the external current in the Hodgkin–Huxley model [3]. The synaptic current I_{syn} describes the interaction of two generators is taken from [4].

Isyn=dypost-ysyn1+exp-ypre-

synksyn 2)

The indices “pre” and “post” correspond to presynaptic and postsynaptic neuron-like generators, respectively, y_{syn} – reverse synaptic potential, θ_{syn} – threshold synaptic function, k_{syn} – steepness of synaptic function, d – synaptic weight parameter.

The single generator was studied numerically by solving equations (1) with Runge-Kutta method, simulated in Simulink environment and in hardware [2,5]. Dynamics of two unidirectionally coupled generators was studied both numerically and in Simulink environment. The aim of the study was to find synchronization regions of two generators with different dynamics.

Results

Synchronization regions of two unidirectionally coupled generators was found by varying parameters γ_2 to control the frequency of the postsynaptic generator and synaptic weight d. Synchronization of spiking, bursting and spiking and two bursting generators has been observed in Simulink model. The areas of synchronization in parameter space have been found.

Hardware implementation of pulse coupling for electronic neuron-like generator connection was developed. The coupling circuit has to reproduce synaptic current function (2). The key features of the function (2) are threshold activation/deactivation and amplitude regulation by synaptic weight parameter d. These features were implemented in electronic circuit in fig.1.

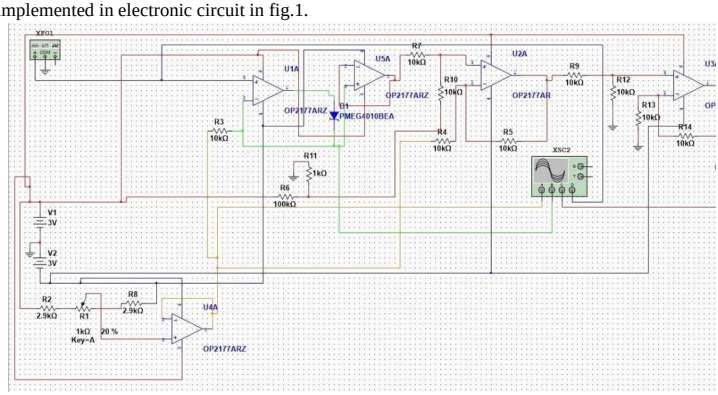

Fig. 1. Electronic circuit for pulse coupling of two neuron-like generators

By changing the resistance value of the resistor R_1, you can set the threshold θ_{syn}, and by changing the resistance of the resistor R_{15}, you can adjust the coupling strength parameter d.

Two electronic neuron-like generators were connected by developed electronic pulse coupling. Synchronous oscillations of two neuron-like generators were observed in hardware in various self-oscillating dynamic modes.

Conclusions

In this work, numerical and experimental studies of synchronization of two neuron-like generators were carried out. Electronic circuit for pulse coupling of two generators was developed and implemented. The proposed coupling circuit allows to build hardware network of spiking neuron-like generators. The coupling circuit could be augmented with adaptive elements (e.g. memristive elements) to modify synaptic weight and reproduce synaptic plasticity effect. This will allow to construct electronic neural networks and neuromorphic processors.

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COGNITIVE NEUROSCIENCE

The section will be an international platform for the exchange of scientific, educational and technical ideas and achievements between specialists, especially young scientists, working in the field of studying cognitive neuroscience. The scope of the section is broad, including research on brain mechanisms underlying attention, memory, spatial cognition, executive function, and social behavior.

FORECASTING OF ADAPTIVE NETWORK'S DYNAMICS BY RESERVOIR COMPUTING

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Introduction and Aims

Forecasting complex systems dynamics is a complicated and important task. Complex systems are characterized by multiple, interacting spatiotemporal scales that challenge classical numerical methods for their prediction and control. In real life, we face the challenges of predicting the dynamics of different natures like weather, climate, economic trends, etc. One of the interesting tasks here is forecasting neurophysiological signals (EEG, for example) to diagnose and react in time to a negative phenomenon, like epilepsy seizure. Recurrent Neural Networks (RNNs) offer a potential method for addressing these challenges. The most promising type of RNN for solving this task is Reservoir Computing (RC)

RC has shown significant success in modelling the full-order space dynamics of high dimensional chaotic systems. In addition, reservoir computers have also been realized physically as optical feedback systems, which can perform chaotic system forecasting at a very high rate.

In this work, we have addressed the question of using RC to forecast the dynamics of the adaptive network, which topology changes in time, and the averaged signal of the network is evolving. A similar process is going in the brain's neural network, and an EEG signal is a macroscopic signal of a group of neurons that connections adapt in time.

Methods

We investigate the signal averaged over 100 Kuramoto oscillators with the adaptation of the couplings. To increase the dimension of the signal, we use delayed signals and reconstruct a phase space.

We use an RC construct known as an echo state network, which uses a network of nodes as the internal reservoir. Every node has inputs drawn from other nodes in the reservoir or from the input to the RC, and every input has an associated weight. Each node also has an output, described by a differential equation. The output of each node in the network is fed into the output layer of the RC, which performs a linear operation of the node values to produce the output of the RC as a whole. We use the reservoir of N = 1000 nodes and investigate RCs with a different number of input nodes.

Results

We find the optimal parameters of the reservoir (spectral radius, nodes degree, input scaling) to achieve a maximal correlation of the output and the target signal. Increasing the dimension of the input signal by adding the delays, we increase the maximum achievable value of correlation, time, and minimal root mean square error of the predicted signal.

We have calculated that the embedding dimension for our macroscopic signal is 4, so the expected dimension of phase space should be 9. Practically, by increasing the dimension up to 9, we achieve the maximal value of correlation, and further increase of the dimension doesn't increase the efficiency of the prediction.

Acknowledgements

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ASSOCIATIVE SEMANTIC LEARNING IN THE DEVELOPING BRAIN: ACTION-PERCEPTION CIRCUITS IN RAPID WORD ACQUISITION

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Introduction

A growing body of literature indicates tight integration between perceptual and motor systems in the adult brain, particularly crucial for the normal functioning of the language system (Pulvermuller & Fadiga, 2010; Vukovic et al., 2017). However, neurophysiological data regarding this linkage in early developmental populations (i.e., young children) is lacking, and neurocognitive mechanisms subserving efficient integration of action and perception in linguistic function during brain maturation and its contribution to the word acquisition processes in early development remain unexplored. The present study used event-related potentials (ERPs) to investigate the effect of sensorimotor (articulatory) training combined with associative semantic learning task in young children.

Methods

Eleven healthy monolingual Russian preschool children (5-7 y.o.) performed a child-friendly word-picture associative learning (so-called *fast mapping*; Vasilyeva et. al., 2019) task accompanied by a brief articulation session. The task employed a counterbalanced set of familiar and novel words presented auditorily in conjunction with novel and familiar images appearing on the screen. A new word's meaning had to be inferred by exclusion from the existing semantic context through a single-shot exposure to the novel item. During the task, the child had to select the new object defined by the previously unfamiliar word form and then articulate the word form overtly three times. Acoustic stimuli were fully controlled dissyllabic (CVCV) word forms of two types: (i) four meaningful Russian words, (ii) four phonotactically and phonologically legal meaningless novel word forms (pseudowords). Visual stimuli consisted of two-dimensional photos of familiar and unknown objects. To define learning-related brain dynamics, passive auditory ERPs to newly learnt words were recorded immediately after the task, with familiar words and untrained pseudowords as control stimuli.

Results

Amplitude analysis carried out for the fronto-central electrode cluster revealed a significant effect of learning, indicating neural activation decrease after the training at 282-322 ms (after the word divergence point) for both familiar and novel words, but not for control word forms, likely reflecting the integration of novel items into the children's mental lexicon. LORETA source analysis indicated that this activity was generated bilaterally in fronto-temporal areas, with maxima in BA21 (familiar items) and BA22 (novel learnt items).

Conclusions

We propose that a single-shot associative word learning task accompanied by brief articulation training leads to an enhanced build-up and/or reinforcement of neural memory traces for both novel and familiar items,

reflecting the developing brain's capacity for rapid acquisition of words with native phonology. Further research is needed to clarify the cortical sources of the learning-related ERP dynamics and to generalize the current result to larger stimulus groups.

Acknowledgements

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ANALYSIS OF THE HEMODYNAMIC RESPONSE IN THE MOTOR CORTEX USING THE FNIRS TECHNIQUE

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The study of the principles and physical laws of the brain is one of the most important and actively studied problems of modern science. One of the most promising and powerful noninvasive neuroimaging tools for recording brain activity is functional near infrared spectroscopy (fNIRS) [1, 2]. This technology uses near infrared light to detect changes in oxygenated (HbO) and deoxygenated (HbR) hemoglobin levels due to hemodynamic brain activity and rapid delivery of oxygenated blood to active cortical areas via the neurovascular junction. It should be noted that fNIRS has the same physiological basis as functional magnetic resonance imaging (fMRI), so both technologies provide interrelated data. At the same time, fNIRS has many advantages: portability, ease of use, real-time monitoring, low sensitivity to motor artifacts, higher temporal resolution, the ability to separately record changes in both deoxyhemoglobin and oxyhemoglobin [3, 4].

This research presents the results of the analysis of the hemodynamic response of the brain when performing various types of movements. The dynamics of oxyhemoglobin, deoxyhemoglobin, total hemoglobin and blood oxygen saturation were considered as analyzed by the signal. The design of the experiment is considered, in which the subject performs two types of movements: single movement - the subject clearly squeezes and unclenches the hand once; a series of movements - the subject clearly squeezes and unclenches the hand several times at a convenient pace for 10 seconds. In this work, we present the results of comparing these types of movement, and also consider various methods for analyzing the hemodynamic response.

The fNIRS data collection and preprocessing procedure were performed using the NIRScout software. It is well known that the experimental data of fNIRS are often influenced by side physiological noises and artifacts, the characteristic frequencies of which are in the frequency range of fNIRS, including Mayer waves (with a typical frequency close to 0.1 Hz), respiration (close to 0.25 Hz) and heartbeat (about 1 Hz). As mentioned in the review article [5], in many cases, bandpass filtering is sufficient to remove low-frequency physiological noise in the fNIRS data. In this regard, a 0.01–0.1 Hz bandpass filter was also applied to the fNIRS signals using NIRScout to prevent the effect of physiological side effects. The arrangement of the optodes was similar to [6] and covered the premotor cortex of M1.

It was confirmed that the distribution of the response when performing a movement depends on the area. It has been shown that the maximum responses appear in the hemisphere contralateral to the performing limb. In this case, the most pronounced response corresponding to the movement of the right hand is located near the position of the C3 EEG sensor. On the contrary, the brightest activity corresponding to the movement of the left hand is located near the position of the C4 EEG sensor. According to recent work [7], these sites coincide with the premotor cortex (M1).

It was found that in the left hemisphere, the right hand elicited a higher response than the left. In the right hemisphere, the response amplitude remains the same for both hands. We hypothesized that the right hand, which is the dominant hand in the group, may require an additional set of neurons in the M1 contralateral cortex. On the one hand, the magnitude of the reaction may depend on the frequency, intensity, or complexity of the motor task. On the other hand, longitudinal training improves laterality towards the activation of the contralateral M1 during left and right-hand movements. Thus, it is assumed that the dominant hand (in this case, the right hand for all subjects) receives extensive training during daily activities. As a result, this can lead to the growth of the motor cortex neuronal ensemble, which supports the dominant hand movements.

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RECONSTRUCTING SINGLE FINGER TRAJECTORIES FROM INTRACRANIAL BRAIN ACTIVITY

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In Brain-Computer Interfacing (BCI), brain activity is recorded and translated into actions intended by the user. Recent developments capitalize on the relation between motor actions and localized activity of motor- and somatosensory regions of the brain. The ability to control a robotic hand or regain control over a paralyzed hand with a motor-BCI has promoted the latter as a solution for patients devoid of voluntary hand control. Electrocorticography (ECoG), an intracranial recording technique, offers new perspectives for such challenging applications as it avoids scarring or other histological processes and combines high spatio-temporal resolution and broad bandwidth with long-term recording stability. What is still lacking is the accurate control of individual fingers, crucial to provide the targeted patient group with a true sense of dexterity. To address this issue, we propose a multiway regression model, called Block-Term Tensor Regression (BTTR), to better account for the multilinear structure of ECoG signals than conventional vector- or matrix-based techniques. BTTR adopts a deflation-based approach sequentially decomposing data into a series of blocks. As the parameters are determined in a fully automatic manner, the model offers increased flexibility and interpretability. We used

BTTR to predict thumb, index and little finger movements (flexions/extensions) from ECoG activity recorded over a subject's sensorimotor cortex. BTTR was trained on joint ECoG/finger movement recordings, the latter obtained with a data glove. BTTR was shown to predict the trajectories of the 3 mentioned fingers with an accuracy of 0.37, 0.87, and 0.78 (Pearson correlation), respectively.

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DOES TRANSCRANIAL MAGNETIC STIMULATION EFFECTS EEG CHARACTERISTICS OF A MOTOR IMAGERY?

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Aims

In this work we tried to look for a way of enhancing ideomotor training by including transcranial magnetic stimulation (TMS) of a corresponding to motor imagery region of the cerebral cortex in it.

The aim of this work was to estimate effects of transcranial magnetic stimulation on electrical activity of the cerebral cortex corresponding to motor imagery.

Methods

This study involved 14 healthy people from 20 to 25 years old (11 women and 3 men). None of them were familiar with motor imagery performance.

To record encephalogram an “NVX-52” amplifier (MCS, Russia) with 32 channels (Fp1, Fp2, F3, Fz, F4, Fc1, Fc2, F7, Ft9, Fc5, F8, Fc6, Fc10, T7, Tp9, T8, C3, Cz, C4, Cp5, Cp1, Cp2, Cp6, Cp10, P7, P3, Pz, P4, P8, O1, Oz, O2) were used, also we recorded muscle activity to monitor proper motor imagery performance. Transcranial magnetic stimulation was performed using “Нейро-МС/Д” (Neurosoft, Russia) with navigation system “Localite TMS Navigator system” (Localite, Germany).

All participants had to take part in two experimental sessions. Both included EEG recording of three tasks: real hand movement, quasi-movement of a hand and imagery hand movement (motor imagery task was performed twice). All recordings were divided into trials – 10 s segments which includes first 5 s of rest (subject is relaxed and does not move or imagining movement) and other 5 s of task performance. Every task recording included 20 trials.

After first session source localization of the maximum desynchronization activity in the cerebral cortex of subjects while doing motor tasks was determined.

All tasks in the second session were performed for the right hand only. In the second session between two motor imagery task recordings, previously determined cortex region was stimulated by 90% of muscle activation threshold power with 5 Hz frequency (1800 stimuli).

Results

Source localization of maximum event related desynchronization (ERD) was determined in the left middle frontal gyrus for the right hand. All subjects were stimulated in that region.

In the second experimental session before-TMS topography of ERD was the same as in first session. After-TMS ERD topography was displaced near to the region of stimulation. Comparing the values averaged over the subjects for each frequency, showed no significant differences in the degree of desynchronization before and after stimulation.

Averaged values of the desynchronization degree for each frequency separately have shown a significant increase after TMS in the ipsilateral hemisphere: in the α-range at 13-14 Hz (Fig.1A), in the β-range - at 15 Hz (Fig. 1B).

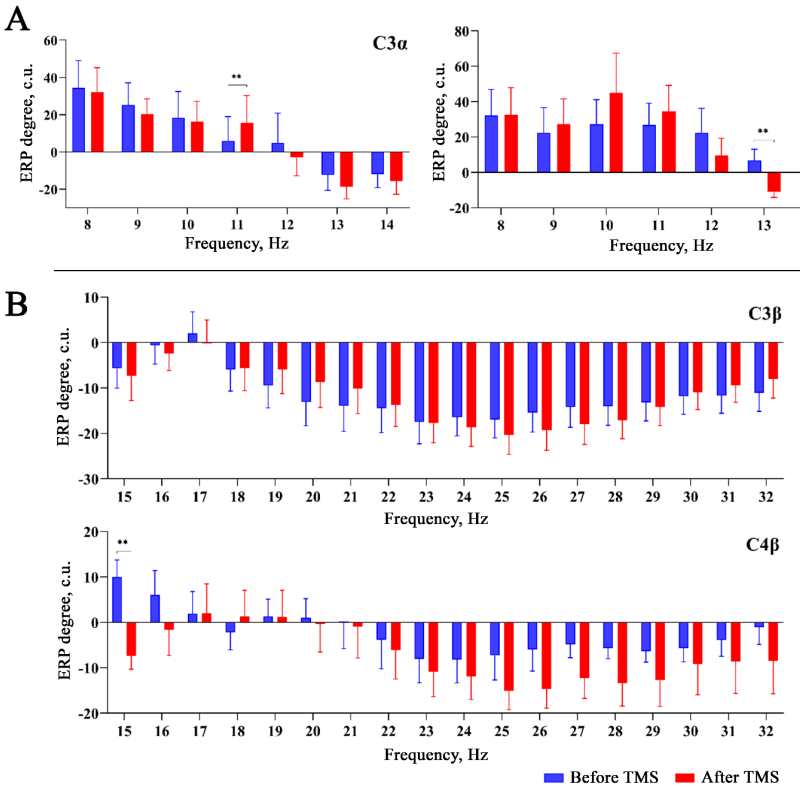

Fig.1. Event related potential (ERP) degrees to frequency relation while right hand motor imagery performance. C3 electrode lies under left side of motor cortex, C4 – under right side. A – relation in α-range, B – relation in β-range. Bars show the mean for the frequency, whiskers – the standard error of the mean. * - p <0.05, ** - p <0.002 (Wilcoxon test).

Conclusion

After-TMS recordings have shown ERD degree increase in ipsilateral cortex regions on certain frequencies, which does not refer to any positive effect. In general, TMS with used stimulation parameters of middle frontal gyrus did not lead to statistically significant difference in desynchronization induced by motor imagery performance. And in this case, stimulation led to an expansion of the area of desynchronization along the cerebral cortex.

MATHEMATICAL MODEL FOR THE DYNAMICS OF THE CARDIOVASCULAR SYSTEM IN THE AWAKE STATE AND DIFFERENT STAGES OF SLEEP

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The study of the dynamics of the cardiovascular system (CVS) during sleep attracts a lot of attention [1], but this dynamic is still largely not understood. It is especially true for the rapid eye movement (REM) sleep, which is associated with higher activation of the sympathetic autonomic control and higher risk of exacerbation of ischemic heart diseases, sometimes even leading to myocardial infarction in coronary artery disease patients [2].

Experimental investigation of the cardiovascular system is significantly limited by the potential risk for the health and safety of the subjects, which limits both the design of active tests and registration of the biological data. Another problem is the overwhelming complexity of the CVS. Studying the CVS using mathematical modeling and numerical experiments is not hindered by these problems and is, therefore, a very valuable field of study.

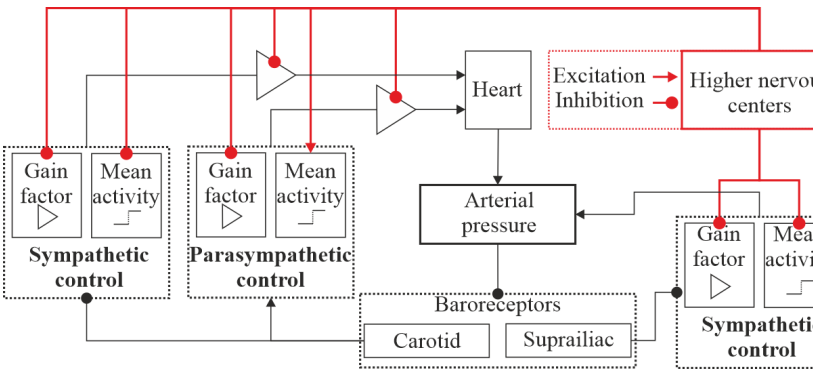

Fig.1. Structure of the model. Elements of the autonomic control are shown in black. The red color shows the inputs from the higher nervous centers

Several mathematical models of the CVS take into account the dynamics of the autonomic control of blood circulation [3, 4], but only a few of them were designed to simulate the CVS dynamics during sleep. The most well-known one is the PNEUMA model [5], but it is an eleventh-order system with more than 80 algebraic terms and more than 200 parameters. This model is undeniably adequate and important, but its complexity hinders the interpretation of the results, and, as stated by the authors themselves [5], no dataset can be used to verify this model. We propose a more compact model [6], its structure is presented in figure 1. We used the ideas proposed in [5, 7] to take into account the influence of the higher nervous centers by adding 8 parameters, which are set equal to zero for the awake state, but they take non-zero values during REM and non-REM sleep to simulate the increase and decrease in autonomic control activity. The proposed model consists of four

differential equations with time delay. The model has 55 parameters, 39 of which have physiological meaning and can be estimated experimentally.

The model was compared to the experimental data from the SIESTA database [8] (20 healthy subjects) using the spectral and statistical analysis of the RR-intervals signals. The results are shown in Table 1. The arterial pressure data are not available in the SIESTA database, but the dynamics of the model agree well with the data from the literature [9]. Despite its compact structure, the model can qualitatively simulate the dynamics of autonomic control during sleep stages and in the awake state and related changes in RR-intervals.

Acknowledgements

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MATHEMATICAL MODELING AND METHODS FOR ANALYSIS THE ELEMENTS OF AUTONOMIC CONTROL OF BLOOD CIRCULATION

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Introduction

The autonomic nervous system (ANS) innervates all organs of the human body. It includes two branches: parasympathetic (including the treelike nerve vagus) and sympathetic (nerve fibers descending along the spinal cord), as well as regulatory centers located in the brain stem [1]. This system plays an essential role in ensuring the normal functioning of a healthy body and, in particular, the cardiovascular system (CVS). Disruptions in the work of autonomic control elements are an important factor in the development of severe pathologies, including neuropathies, arterial hypertension, asthma, etc. The activity of ANS elements can be assessed in non-invasive experiments during the analysis of CVS signals [2]. However, the implementation of diagnostic methods is hindered by the lack of fundamental knowledge about the features of the collective dynamics of ANS elements and their interaction with other body systems. In addition, the experimental signals are non-stationary, noisy, and

are highly irregular. Therefore, to analyze them, it is necessary to develop specialized methods. This paper presents some of our developments aimed at solving these problems.

Methods and Results

We have previously shown that the autonomic control loops of heart rate and mean arterial pressure, as well as the activity of their control centers (located in the brain stem) can be synchronized with a respiration signal, the frequency of which varies linearly with time [3]. These results indicate that these regulation loops can be considered as interacting autogenerators influenced by the respiration signal.

Such conclusions made it possible to investigate the synchronization between the indicated autonomic control loops. However, due to the nonstationarity of signals and the complexity of the dynamics of the systems under study, for this it was necessary to develop a specialized method [4]. The results obtained indicate that the studied loops demonstrate long intervals of phase synchronization alternating with periods of asynchronous behavior. At the same time, the synchronization time of the contours reflects the state of health of the subjects and correlates with their age [5-7]. It has been shown that the calculation of the proposed synchronization measure makes it possible to assess the state of subjects who have suffered myocardial infarction [8], to personally choose drug therapy for arterial hypertension [9], and provides important fundamental information about the organization of the coupling structure between the elements of autonomic control when analyzing patient signals during cardiac surgery [10].

The results obtained made it possible to create mathematical models of the CVS, taking into account the nonlinear dynamics of the autonomic control loops. The models made it possible to explain one of the mechanisms of the development of arterial hypertension [11], the chaotic dynamics of the heart rate [12], the peculiarities of the CVS dynamics during physiological tests [13] and when falling asleep [14].

Conclusions

The development of methods for coupling and synchronization analysis of autonomic control loops of blood circulation and centers of their control in the brain stem made it possible to obtain important fundamental results on the functioning of the circulatory system. On the basis of the results obtained, mathematical models of CVS were created, which made it possible to explain the peculiarities of the complex nonlinear dynamics of CVS elements in normal conditions, with the development of pathologies and when exposed to autonomic control by higher nervous activity, in particular, at various stages of sleep.

Acknowledgements

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THE BRAIN NEURONAL ACTIVITY OF CHILDREN AND ADULTS DURING SCHULTE TABLE TASK COMPLETION

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Introduction and Aims

Neuropsychological and behavioral performance in daily activities mostly relies on the interaction between different cognitive functions rather than their particular aspects. Goal-directed behavior requires sensory information processing and decision making to give a reasonable behavioral response. On the one hand, our decisions depend on the quality of sensory input. On the other hand, they are affected by top-down mechanisms, including context-related expectations and prior knowledge. Thus, substantial evidence or high capacity of the top-down component reduces cognitive demands at the decision-making stage and facilitates the decisions. The evidence accumulation process involves different cognitive functions. For instance, selective attention allows focusing on decision-relevant features and tuning out unimportant details. Cognitive control also aims at prioritization of relevant over the irrelevant information. Working memory maintains these priorities, so that processing resources are allocated with a higher priority to the relevant information. Mechanisms of interaction between the cognitive processes during the mental tasks change with age. Uncovering the way, they change will substantially complement and advance our knowledge about brain development.

To address this issue, children and adults to the Schulte Table (ST) with simultaneous recording of their EEG and response time. ST represented a matrix of 5x5 randomly arranged numbers from 1 to 25, and a task was to find all these numbers in descending order as fast as possible. We supposed that performing this task relied on several cognitive processes, including visual search, working memory, and mental arithmetics.

Methods

Experimental design suggested that the subject performed specific cognitive task and EEG signals were recorded during this process. There were two groups of participants: (i) children (age 7-8) and adults (age 18-20). Cognitive task was to accomplish ST – simplified version of Zahlen-Verbindungs-Test (ZVT), widely used in Russia. Schulte test consisted of matrices (tables) of 5x5 randomly arranged numbers from 1 to 25. The subject was asked to find numbers in a descending order from 25 to 1 by pointing each found number with the Tablet PC and stylus. We registered time moments corresponding to pointing each number in the table. Also, we recorded EEG signals.

Results

We demonstrated that adults accomplished ST faster than children. However, this difference diminished at the end of table completion. In children, EEG analysis revealed high parietal alpha-band power at the end of the task. It might indicate the shift from procedural strategy to less demanding fact-retrieval. In adults, the frontal beta-band power increased at the end of the task. It might reflect enhanced reliance on the top-down mechanisms, cognitive control, or attentional modulation, rather than a change of arithmetic strategy. Finally, the EEG power of adults exceeded one of the children in the left hemisphere, providing potential evidence for the fact-retrieval strategy. When the numbers became one-digit, children reduced search time by 70%, which is significantly higher than adults. We hypothesized that arithmetical problem size was the main factor limiting the completion speed of children. Children experienced difficulties at the beginning when operating with two-digit numbers. However, for the one-digit numbers, their performance increased and reached adults' scores at the end of completion.

Our findings contribute to the analysis of interaction between the cognitive processes during the mental tasks for different ages. We also discuss our findings in the context of early school math teaching.

THE INFLUENCE OF STRESS DURING INFANT AND JUVENILE AGE PERIODS ON YOUNG ADULT BEHAVIORAL PHENOTYPE OF C57BL/6 MICE

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Aim

Psychological stress can help child to take the experience about different life situations. At the same time, early childhood and teenage years are critical periods of individual development when stress situation can influence with serious consequences such as developmental disorders or exacerbation of the disease. The aim of this research is to learn and analyze the influence of different stress models used during infant and juvenile age periods to behavioral phenotype of young adult C57Bl/6 mice.

Methods

The study was performed on of the C57BL/6 mice (males). Maternal separation (MS) modeling consisted of maternal separation for 4 h (PDs 2-5), 8 h (PDs 6-16) and final weaning on PD 17. The social defeat model (SD) was realized on 20-29 PDs with using of the aggressive resident mice for modeling of daily physical and emotional stress. Neuroinflammation (NI) was modeled on PD 17 by i.c.v. injections of 0,5 μg/kg of LPS (in 2 μL of saline), saline injections were administered to control group. The investigation of behavioral phenotype were produced on PDs 31-35.

Results

With the Open Field Test mice of MS group demonstrated the increase of mean speed and distance that is the evidence of hyperexcitability. At the same time, SD and NI groups showed the decrease of activity. Moreover, mice of all groups demonstrated the aberrance of interest to objects with the Novel Object Test in comparison with intact group. The social memory was disordered for all groups that shows of the changes of the emotional status. The most significant difference was registered with Passive Avoidance Task. Mice of MD and NI groups showed the lack of working memory, they have not learnt for the reflex. At the same time, the best results of passive avoidance test showed SD group, the significant increase of latent period in comparison with intact group was registried. The passive avoidance test has showed the depressive-like behavior for MD group, but NI and SD animals demonstrated only low activity level.

Conclusion

There was discovered a number of consequences of different models of stress used during infant and juvenile age periods. The maternal separation of infants leads to hyperexcitability and decrease of attention, neuroinflammation of juveniles cause the decrease of activity and social interest, and both models lead to serious lack of working memory for forming of reflexes. On the contrary, social defeat stress is the reason of changes of social memory, but the working memory improves. All of these changes can influence to quality of adult life.

EEG CORRELATES OF VISUOMOTOR TRANSFORMATION WITH A P300 BRAIN-COMPUTER INTERFACE FOR POST-STROKE REHABILITATION

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Brain-computer interfaces (BCIs) are increasingly used for post-stroke rehabilitation. Here we consider a therapeutic P300-based BCI, where flickering visual stimuli represent potential motor targets. With this approach, voluntary movements are enabled toward visual targets in post-stroke patients to facilitate rehabilitation. Our neurorehabilitation approach comprises appropriate computational algorithms, a virtual reality (VR) setup that displays targets of reaching movements, a P300 BCI for extracting target information from EEG activity, and a robot that moves the stroke-affected arm toward the instructed target. While this system operates reliably in both healthy subjects and stroke patients, offline EEG analysis is needed to understand the rehabilitation process better. Here we suggest an analysis of EEG patterns across the training sessions, which incorporates quantification of evoked responses to targets and non-targets and an assessment of evoked and induced changes in the EEG alpha rhythm. We have applied these analyses to the data from a small number of patients examined so far (N=7) to obtain individual profiles of their rehabilitation course. We suggest that our methods be utilized in the analyses of visuomotor transformations assisted by a BCI – a novel approach capable of engaging multiple cortical areas and inducing therapeutic neuroplasticity.

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MODELING METASTABLE VISUAL PERCEPTION AND NEUROPHYSIOLOGICAL EXPERIMENTS

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Visual perception is the process of creating virtual images in the brain conforming to incoming information and existing experience. In case of receiving an ambiguous stimulus, the brain interprets it depending on the context, i.e. in accordance with previous information. Therefore, the brain can be considered as a metastable dynamical system, the current state of which depends on the initial conditions, and the switching between coexisting metastable states is caused by an inherent stochastic process in the neuronal network or endogenous brain noise. Thus, an adequate mathematical model of visual perception should take into account two important issues: the deterministic process of the neural network adaptation and noise-induced switching among possible mental states.

In this lecture, mathematical models and modern experimental approaches for studying metastable visual perception are discussed. The results of numerical modeling are compared with neurophysiological experiments based on electro- and magnetoencephalography.

RECURRENCE QUANTIFICATION ANALYSIS FOR SINGLE TRIAL P300 DETECTION

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The present research aims at demonstrating an approach to detect event-related potential P300 on the single-trial EEG based on recurrence quantification analysis (RQA) of the EEG signal complexity. P300 is a positive deviation of EEG signal amplitude at approximately 300 ms after the visual, auditory, or tactile command and is often associated with decision making and stimulus recognition [1-3]. Traditionally, P300 is well-observed at averaged EEG data [4]. At the same time, a considerable amount of research recognises P300 as a relevant marker for ERP-based brain-computer interfaces (BCI), which makes its detection on single-trial EEG a relevant and social significant task [5-7].

Methods

We show that RQA measures of complexity can detect P300 on single trials by analyzing the dynamical properties of EEG signals. RQA uses the well-known feature of many dynamical systems to return to the previously visited states [8]. Assessment of such recurrences in corresponding time series reveals qualities of the systems' dynamical behavior [9]. In the present research, we use a recurrence times-based measure to detect transitions between chaotic and periodic regimes (and vice versa) in EEG signals associated with the P300 potential. Thirteen healthy young adults participated in a single sensorimotor integration training session, during which they performed simple motor tasks with upper limbs under the auditory cue.

Results

First, we used a spatiotemporal permutation test based on random partitions to highlight the cluster of significant neural activation associated with P300. Next, we demonstrated that RQA measures detect the changes in EEG signal complexity during P300 and are sensitive enough to identify P300 on single-trial EEG. We emphasize that the most significant result was achieved via a measure of recurrence time entropy, which is a relevant quantifier of chaotic-periodic and periodic-chaotic transitions [10].

Conclusions

We proposed an approach for single-trial P300 detection based on extracting the EEG signals' complexity features using RQA. We demonstrated that recurrence times-based measure of complexity is sensitive to dynamical transitions on single-trial EEG. The considerable accuracy rate suggests that RQA-based measures of complexity can be considered as an appropriate choice for a BCI-based ERP detection system.

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NEURONAL ENCODING OF OBJECTS AND SPACE IN HIPPOCAMPUS: NEW APPROACH IN VERIFICATION OF NEURONAL SPECIFICITY

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Aims

Neuronal encoding of environmental information has long been in the focus of neuroscience. Neurophysiological studies show that when animals become familiar with space or objects, neuronal activity changes due to these factors. However, despite a considerable amount of experimental data, the specific neural bases of space and objects encoding remains an open question. The goal of the present study was to investigate how the hippocampus encodes information about space and objects at the level of individual neurons, to determine stability and variability cognitive maps over time and over presentation of novel objects.

Methods

For this purpose, we developed an approach combining optical calcium imaging of neuronal activity and assessment of animal behavior during novel object recognition (NOR) task. The novel object recognition test, is a relatively fast and efficient means for testing different phases of learning and memory in mice. It was originally described by Ennaceur and Delacour in 1988 and used primarily in rats [1]; however, since then, it has been successfully adapted for use in mice [2]. The test relies on as few as three sessions: one habituation session, one training session, and one test session. Training simply involves visual exploration of two identical objects, while the test session involves replacing one of the previously explored objects with a novel object. Because mice have an innate preference for novelty, a mouse that remembers the familiar object will spend more time exploring the novel object [3].

To record neuronal activity we used nVista HD head-mounted miniaturized microscope [4], we visualized neuronal calcium activity in the CA1 field of the hippocampus of freely moving mice in the novel object recognition task. We installed the nVista microscope over the microendoscope lens implanted in the hippocampus of mice previously transduced with rAAV particles carrying GCaMP7f green calcium indicators under the control of the CAG promoter. A total of 5 C57Bl/6 mice, aged 3-10 months at the start of imaging, were used in this study. Mice were individually housed in cages in a 12:12 h light cycle and food available ad libitum.

The extraction of the calcium signal was carried out using the own software developed by the authors in the MATLAB packages using the Mosaic 1.2 toolbox (Inscopix). Processing steps included motion correction, signal normalization, isolation of cellular components by the principal and independent components analysis (PCA / ICA), artifacts removal, light-corrected signal extraction and detection of significant calcium events. To determine the fields of place cells, the authors proposed a new approach based on determining the spatial information content of the field.

Results

The protocols were developed for calcium imaging of the hippocampus of mice with NVista HD head-mounted miniscopes and also methods for neural activity data processing, which allow identifying specific locations of neurons and time series of their activity, as well as protocols for video tracking data processing. The algorithm for video tracking of animals in the Bonsai visual programming environment was developed, which

allows to reliably detect the position of animals in the experimental cage. Additionally, a complex of software tools was developed in the MATLAB and Python environment to ensure synchronization, analysis and visualization of the obtained data.

The neuronal activity of a hippocampus was recorded during all sessions of novel object recognition task. The calcium signal was successfully extracted from 5 mice, a total of more than 900 neurons were isolated (with at least n = 3 calcium events), more than 700 neurons had fields satisfied the criteria for spatial information content, for these fields were defined specializations in relation to space and objects. Distributions of place fields in space (cognitive maps) were built for each mouse. It was shown that cognitive maps are uniformly distributed throughout the cage space and are not tied to specific landmarks, excluding areas of objects. Although the object areas cover a smaller fraction of the cage's space, there were significantly more neurons with object place fields than neurons with place fields. We have shown that difference in quantity distribution of object place fields is not observed upon presentation of objects the same novelty. However, presentation of both familiar and novel objects leads to an increase in the number of fields specialized for the novel object.

Conclusions

We have shown that the activity of hippocampal neurons exhibits specificity of the position of the mouse in space, as well as in relation to novel and familiar objects that indicates the formation of a space and objects cognitive map. It was shown this map exhibits both stability over time and variability with respect to the presentation of novel objects. The presentation of both familiar and novel objects leads to an increase in the number of neurons specialized for the novel objects.

Acknowledgments

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A PROTOCOL FOR ASSESSING SPATIAL ORIENTATION BEHAVIOR IN RATS EXPOSED TO CONDITIONAL ULTRASOUND

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Spatial orientation is of vital importance for animals. In higher animals and humans, it relies on cognitive maps and spatial memory [1]. Yet, its neural mechanisms are not fully understood due to a large number of neuronal circuits involved in information processing. Therefore, one of the emerging problems in Neurobiology is the experimental and theoretical studies of the dynamics of neural networks in cognitive navigation tasks.

The hippocampus is one of the brain regions involved in the building of cognitive maps. About 40% to 60% of the pyramidal neurons in the CA1 region are place cells that selectively respond to the specific position of an animal in space [2]. Experimental findings have stimulated theoretical studies. Recently, a spiking neural network model has been proposed to mimic the dynamics of place cells [3]. The model implements the spatial memory embedded in an animat that moves and explores an arena. The arena has safe and dangerous areas, and the animat can learn their location to avoid unsafe regions. However, as it has been shown, the learning is not

perfect. Even after training, the animat eventually visits dangerous areas. Such unperfect learning allows retraining in time-changing environments and ensures an adaptive behavior.

In this work, we aim at testing experimentally in rats the theoretically found behavior. To do this, we developed a protocol for conducting a behavioral study of spatial memory in the task of learning dangerous regions. The setup consists of a cylindric cage of 120 cm in diameter with four black lines on the cage floor for visual conditioning. These lines divide the field into four equal sectors. For additional orientation of the rat in space, there is a visual cue in the form of a black rectangle located on the sidewall of the cage. We used an ultrasonic signal with a frequency of 23-25 kHz, duration of 0.5 s, and amplitude sufficient to evoke a feeling of fear in a rat when it enters a sector of the arena designated as a dangerous one. Then, the rat had to move to another "safe" sector to avoid exposure to the painful sound.

We used six Sprague Dawley adult rats (6-month-old). At the beginning, a rat got used to the setup for 10 minutes by freely moving and exploring the entire field. During this time, the animals visited the “dangerous sector” (no ultrasound has been applied) on average ten times. The average time spent by the rats in this area was 84 s. Then, we switched on the negative stimulus when a rat was entering the danger zone. The learning session lasted for 10 min. After 24 hours, 48 hours, one week, and two weeks, the animals were placed again in the setup. In each session, the orientation behavior of the rats was observed for 10 minutes switching on the negative stimulus upon entering the dangerous sector. After training, the animals avoided the dangerous sector in the setup. Still, eventually, the rats tried to enter the stimulated zone and quickly ran away from it after the ultrasonic stimulus was applied.

Our results show that rats can associate an irritating ultrasonic stimulus with a dangerous zone and avoid it after learning. Moreover, as the theory predicted, the rats still try time-to-time to enter the danger zone after training. This behavior enables adaptive changes necessary for survival. If the danger zone moves to a different location, the animal can relearn and reassign the position of safe and dangerous zones.

Acknowledgments

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EFFECTS OF HTR7 GENE OVEREXPRESSION IN MIDBRAIN FOLLOWED PROLONGED ETHANOL EXPOSURE ON BEHAVIOR AND BRAIN 5-HT SYSTEM OF C57BL/6J MICE

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Aim

The serotonin (5-HT) system is involved in the regulation of a variety of normal and pathological behaviors, including ethanol-induced affective disorders. However, the neurobiological processes underlying between alcohol-induced pathological behavior are poorly understood [1]. Prolonged ethanol consumption is known to reduce the functional activity of brain 5-HT system. Among many hypotheses for the appearance of affective disorders, the 5-HT hypothesis is still the subject of special attention. Of great interest are the 5-HT_{1A} and 5-HT_7 receptors, which can form heterodimers in the midbrain, that likely leads to the internalization of the presynaptic 5-HT_{1A} receptor, leading to elevation of 5-HT level in the synaptic cleft [2]. The aim of the study

was to examine behavior and changes in the brain 5-HT system after overexpression of the *Htr7* gene encoding 5-HT_7 receptor followed prolonged ethanol exposure.

Methods

The research was carried out on adult C57Bl/6J male mice. The stereotactic injection of adeno-associated viral particles carrying pAAV_Syn_HTR7-EGFP plasmid in the midbrain resulted in the overexpression of 5-HT_7 receptor fused with EGFP. After injection mice drank 10% ethanol for 6 weeks. 4 experimental groups were utilized: «PBS-injected/water», «PBS-injected/ethanol», «EGFP-injected/ethanol» and «HTR7-EGFP-injected/ethanol». The behavior was evaluated in the open field (OF), forced swim test (FST) intermale aggression, novel object recognition (NOR), and dark-light box (DLB) tests. *Htr1a, Htr2a, Htr7, Slc6a4, Tph-2* genes expression levels were estimated by quantitative real-time PCR. 5-HT_{1A}, 5-HT_{2A}, 5-HT_7, TpH2 and 5-HTT protein levels were assessed by Western-Blotting. Mean values were compared using one-way ANOVA followed by Fisher`s LSD post-hoc comparisons.

Results

Injection of AAV_Syn_HTR7-EGFP led to overexpression of *Htr7* gene mRNA and 5-HT_7 protein levels in midbrain that decreased ethanol-induced level of intermale aggression enhancement at the trend level. Anxiety level in DLB was increased only under the influence of alcohol and 5-HT_7 overexpression in the midbrain failed to affect it. Neither prolonged ethanol consumption nor 5-HT_7 overexpression affected the behavior in OF and NOR tests. 5-HT_7 overexpression in the midbrain reduced ethanol-induced 5-HT_{1A} protein level elevation in the midbrain while there were no changes in frontal cortex and hippocampus. Chronic ethanol caused TpH2 protein level decline and 5-HTT protein level elevation in the midbrain. The mRNA level of *Htr1a* gene was affected only by prolonged alcoholization: an increase in midbrain and a decrease in the frontal cortex and hippocampus were found. Chronic alcoholization produced elevation of *Htr2a* gene mRNA level in frontal cortex.

Conclusion

Prolonged ethanol consumption increased intermale aggression level which was reduced due to 5-HT_7 overexpression in the midbrain at the trend level. Observed effect was accompanied by decline in the level of 5-HT_{1A} protein in the midbrain. These results are consistent with the hypothesis on upregulation of the functional activity of brain 5-HT system due to 5-HT_{1A}/5-HT_7 heterodimerization in the midbrain induced by 5-HT_7 receptor overexpression.

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RESEARCH OF SENSORY INTEGRATION MECHANISMS AND INFLUENCE ON THE AMBIGUOUS IMAGES PERCEPTION

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Studying the processes of brain processing of signals received from the senses, also known as sensory integration, makes it possible to analyze the mechanisms of the human brain and the ways of making decisions. Understanding these processes can help develop new therapies for people with sensory integration dysfunction,

which is estimated to affect one in twenty children and leads to disorders such as attention deficit hyperactivity disorder, autism, or dyslexia [1].

One of the methods for studying the sensory integration can be the study of the procedure of processing sensory information during a long-term cognitive task. This kind of task can be the perception of ambiguous images, in particular - Necker cubes [2,3]. In practice, the processes involved in the perception of ambiguous images can be analyzed by recording the electrical activity of the cerebral cortex using electroencephalography.

Aims

The aim of this work was to study the processes of sensory integration when people perceive ambiguous images, in particular Necker cubes.

Methods

The study involved 30 healthy subjects (16 women and 14 men) aged 20-25 mean ± standard deviation 21.8 ± 1.4). Subjects completed the Multidimensional Fatigue Inventory test before and after the session. EEG signals were recorded using a certified NVX 52 amplifier (LLC "Medical Computer Systems," Russia) with 32 Cl/Ag electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, Ft9, Fc5, Fc1, Fc2, Fc6, Fc10, T7, C3, Cz, C4, T8, Tp9, Cp5, Cp1, Cp2, Cp6, Cp10, P7, P3, Pz, P4, P8, O1, Oz, O2), positioned according to the standard international 10-10 system. The combined earlobe electrodes were used as a reference. The grounding electrode was placed on the forehead. All electrode impedances were kept below 15 kΩ. EEG was digitized with a signal sampling frequency of 1000 Hz and filtered in the frequency range from 1-100 Hz with a 50 Hz Notch filter.

The session consists of 400 Necker cubes images presented with varying degrees of ambiguity (0.15, 0.25, 0.4, 0.45, 0.55, 0.6, 0.75, 0.85), which corresponded to the intensity drawing the edges of the cube.

Cubes with a degree of ambiguity up to 0.45 inclusive are left-oriented, and cubes with a degree of ambiguity from 0.55 are right-oriented. Cubes with degrees of ambiguity 0.4, 0.45, 0.55, 0.6 are considered highly ambiguous cubes - their direction is more difficult to determine. The cube with each degree of ambiguity was presented 50 times. Each image was displayed for 1-1.5 seconds, between images a neutral background was presented for 3-4 seconds.

Upon presentation of the cubes, the subject had to press the button with the left or right arrow on the remote control, depending on which cube (left- or right-oriented) he saw.

Also, to synchronize the time of the presentation of the cube, pressing the button and EEG stream we used LED sensor placed on the screen at the monitor corner.

Results

The performance of a more complicated task as known leads to more errors. In particular, the classification of less ambiguous right- or left-oriented cubes (LA task) is more accurate than highly ambiguous Necker cubes (HA). As a result, the median accuracy for LA tasks (M = 88%, SD= 0.14) was higher than to HA stimuli (M = 75%, SD = 0.17).

The analysis did not reveal the influence of degree of cube ambiguity on the reaction time. Median reaction time for LA tasks (M = 0.727 s, SD= 0.16) was not statistically lower than to HA stimuli (M = 0.731 s, SD = 0.15). The difference between these results and those described in the literature can be explained by the fact that in our work the subjects had not previously encountered the stimuli presented to them. Thus, the complexity of the task for the subject did not change depending on the degree of ambiguity of the stimulus.

Conclusions

In this study we analyzed the recognition accuracy of complicated task and it was shown that less ambiguous Necker cubes are easier to determine than highly ambiguous with the same reaction time. At the same time, right-oriented cubes with a high degree of ambiguity were recognized worse than left-oriented ones; the lowest accuracy was observed at recognizing cubes with a degree of ambiguity of 0.55 (average accuracy - 72%), which indicates that the subjects really perceive Necker cubes by default as left-oriented.

Also, during the experiment, a decrease in the response time to stimuli was observed as the number of stimuli demonstrated increased, despite an increase in the subjects' fatigue towards the end. This is indicative of the learning effect.

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SENSORY SUBSTITUTION OF VISION: AN OVERVIEW

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From the very beginning, sensory substitution technology was conceived as a technology to improve the quality of life of the people with disabilities of any sensory system. Most often it concerns the vision. The idea is to use special equipment sensory substitution devices (SSDs) to convert the video signal from the camera in an appropriate way and pass it to the input of one or more intact sensor systems [1]. This approach assumes that the brain, possessing neuroplasticity, in the process of special training can learn to the perceive and navigate in the world of physical stimuli more effectively and, thus, partially compensate for the dysfunction of the damaged sensory system.

The aim of this work is to overview the field of non-invasive sensory substitution techniques.

In this work, we used the results of published experimental and review works on sensory substitution. The search was carried out in the Web of Science, Scopus, and other scientific citation databases. Some of the materials were obtained from the websites of companies dealing with equipment for sensory substitution. Keywords were selected using relevant controlled vocabulary: sensory substitution, multisensory substitution, sensory substitution device, data preprocessing, visual impairment and blindness.

This overview shows that although there are several working and marketable sensory substitution systems, problems remain that prevent their widespread use [2]. First, sensory substitution devices are narrowly focused, and inclusive design may be the solution [1]. Second, there is the problem of learning how to use sensory substitution devices: this is a long process that can last from several months to several years [2, 3]. Third, the experiments exist in laboratory conditions and require transfer to real environments [4, 5]. In addition, there is another problem of a semantic confusion concerning the use of terms in the field of sensory substitution [1].

The authors believe that the increase in the efficiency of sensory substitution devices can lay in the field of data preprocessing obtained from the sensing device – in the case of vision, it is a video camera. We mean that some part of the data analysis work should be performed by artificial intelligence systems embedded as a component in SSDs.

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EMG-INTERFACE BASED ON A SPIKE NEURAL NETWORK

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The Human-Machine Interface (HMI) is crucial in the development of control systems for medical rehabilitation devices, such as artificial limb and exoskeletons. HMIs based on biomimetic signals such as electromyography (EMG) are commonly used in this area. At the same time, one of the current trends in the development of HMI is the involvement of spiking neural networks (SNNs) in signal processing (Lobov et al., 2015, 2020). SNNs can be trained by bio-inspired algorithms based on Hebbian learning, such as experimentally verified effect of Spike Timing Dependent Plasticity (STDP).

Recent study suggested an SNN which is able to classify simple EMG patterns in the context of both supervised and unsupervised learning (Lobov et al., 2020). However, a completed SNN-based EMG interface for controlling external devices previously has not been presented.

Aims

Development and testing of SNN-based EMG interface for robot control.

Methods

We used the phenomenological model of Izhikevich's neuron to implement the dynamics of spiking neuron. The SNN included two layers of neurons - sensory (S) and classifying (C). The S-layer performed a sensory function and the C-layer classified the EMG patterns after training.

We used a MYO Thalmic bracelet with 8 channels to register EMG patterns. Signals from each EMG channel were transmitted from electrodes of the bracelet to neurons of S-layer (S-neurons). The value of the stimulating current was proportional to the amplitude of the EMG signal and corresponded to the muscle effort under the corresponding electrode of the bracelet. The bracelet was placed on the subject's forearm. In the process of SNN training, each subject performed hand gestures in sitting position for one minute.

For training the SNN, we used supervised and unsupervised learning. In the first case, a target C-neuron was under go by high frequency (40 Hz) stimulation during fulfilment of some hand gesture. After training, this neuron could classify the corresponding gesture. In contrast to this case, in unsupervised learning, it was a priori unknown which C-neuron would classify a given gesture.

The study involved 15 healthy subjects. The accuracy of classification of EMG patterns was calculated as the rate of spikes of the C-neuron corresponding to the EMG pattern to the total number of spikes of all C-neurons. Considering the distribution that does not correspond to the Gaussian we used the nonparametric Mann-Whitney test. Differences between groups were considered significant if the level of statistical significance was $p < 0.05$.

Results

During the study, the subjects performed “simple” (hand flexion and extension) and “complex” (adduction and abduction of the hand in the wrist joint) gestures. The classification accuracy of simple EMG patterns was, as expected, higher than the classification accuracy of complex patterns. In the case of classification of complex EMG patterns, we found a significant ($p = 0.02$) increase in accuracy with supervised learning than with unsupervised learning. In general, in the case of simple EMG patterns there were no significant differences in the classification accuracy with supervised and unsupervised learning. However, at the same time, the relaxation patterns were classified by SNN after supervised learning significantly ($p = 0.04$) better than after unsupervised learning.

To implement the HMI, we connected an external device (the LEGO robot) to the trained SNN. For this purpose, we added the motor M-layer to the classifying C-layer. Each M-neuron corresponded to a certain direction of movement of the robot: go straight, right, left.

To test the HMI, the subjects controlling the robot participated in the race with obstacles. When using SNN after supervising learning, the average race time was less than when using SNN after unsupervising learning. Even in the case of using simple EMG patterns, despite no significant differences in classification accuracy, the race time was reduced.

Conclusion

As a result of the study, in the case of complex EMG-patterns, we obtained significant increase in the classification accuracy of SNN after supervised learning in comparison with unsupervised learning. We have implemented a SNN-based EMG interface to LEGO robot. In the cases both complex and simple EMG-patterns, when using SNN after supervising learning, the average race time was less than when using SNN after unsupervising learning.

Acknowledgements

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SYNCHRONIZATION OF METASTABLE OSCILLATIONS IN EVOLUTIONARY GAMES

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Aims

Evolutionary game theory studies the behavior of populations whose members constantly involved in strategic interactions. Within the game theory framework, the famous gender conflict over parenting was formalized by Dawkins in the “Battle of Sexes” (BoS) game [1], in which members of the opposite-sex population play (interact). Each player has two behavioral strategies that reflect attitudes towards creating a family and raising offspring. After using a certain strategy, the player gets a payoff, which also depends on the strategy chosen by the opponent. Over time, both populations change their composition: individuals are born and die. The dynamics of the system is considered before extinction, which implies that in one of the populations there are players with only one strategy.

For this system, it was shown that absorbing states (complete dominance of one of the strategies for choosing a partner) are achieved only at asymptotically large times and do not reflect the important properties of the transition dynamics in the system. In this regard, metastable (quasi-stationary) states were studied, in which the system can remain for a long time before entering absorption state. As a result, metastable oscillations in the number of players with the first/second strategy (nonlinear stochastic oscillations with a finite lifetime) are observed in the system [2, 3].

It turns out that in the real world, many species have mating strategies and preferences that change with the seasons. In the BoS game, this behavior can be modeled by periodic changes in payments. This raises an important question about the synchronization of metastable oscillations as well as the possibility of controlling the properties of such oscillations (amplitude and lifetime) by an external periodic signal.

Methods

The state of the system under consideration is described by two quantities, *y* and *x*, characterizing the proportion of players with the first strategy in the male and female populations.

For numerical simulating Langevin stochastic differential equations representing the dynamics of variables *y* and *x* are used [3]. Using the Monte Carlo method, the Langevin dynamics of the system is modeled, namely, the trajectories of changes in the state of the system over time are calculated. The resulting trajectories are used to determine the oscillation period, phase, metastable state lifetime and synchronization state.

By changing the amplitude and frequency of the external periodic signal, we determine the synchronization region in which the frequency of the forced oscillations of the system is equal to the frequency of the external influence.

Results

Carrying out the necessary experiments, we found that the frequency locking region expands with an increase in the amplitude of the external periodic signal. However, the sync region is asymmetric with respect to frequencies. In addition, we observed that the amplitude and the lifetime of metastable oscillations depend on the presence or absence of synchronization. In particular, in the synchronization mode, with an increase in the modulation amplitude, the amplitude of the system oscillations increases, and the lifetime decreases.

Conclusions

We have shown that in the considered evolutionary BoS game there is a possibility of synchronizing metastable oscillations with an external periodic signal. Moreover, the amplitude and lifetime of metastable states can be controlled by choosing the parameters (amplitude and frequency) of the external signal, including outside the synchronization mode. In other words, modulation can be used to control the behavior (choice of strategies) of players. The obtained scientific results reveal a new aspect of the fundamental phenomenon of synchronization.

Acknowledgements

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THE EFFECT OF SYSTEMIC INFLAMMATION AND ACUTE INFLAMMATION IN THE LONG -TERM PERIOD ON COGNITIVE FUNCTIONS IN C57BL/6 MICE

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Epidemiological studies show that chronic inflammation is positively correlated with the development of neurodegenerative processes and cognitive deficits in the elderly. Moreover, according to the latest data, it has become known that peripheral infections accompanied by inflammation are the main risk factors for the development of sporadic Alzheimer's disease and Parkinson's disease.

Currently, one of the most widely used animal models of peripherally induced neuroinflammation and neurodegeneration is the administration of lipopolysaccharide (LPS) - an endotoxin of gram-negative bacteria. In

this regard, the aim of this study is to compare the signs of neurodegeneration in physiological aging and in the simulation of chronic neuroinflammation in 4-month-old C57BL/6 mice.

To simulate chronic systemic inflammation, intraperitoneal administration of bacterial lipopolysaccharides (LPS) of Escherichia coli 0111:B4 (Sigma Aldrich) was performed at a dosage of 0.5 mg/kg every 3 days for 3 months. The effects of acute inflammation in the long-term period were also modeled by a single administration of LPS at a dosage of 5 mg/kg. After that, the animals were in a state of rest for 3 months until the moment of behavioral testing. The comparison groups were 4-month-old animals with chronic intraperitoneal administration of saline solution (control) and a group of 18-month-old animals of the same line (regarded as having reached a period of pronounced senile changes). The animals were kept in standard vivarium conditions and underwent behavioral phenotyping procedures.

According to the results of the "Open Field" test, it was revealed that only the group with chronic neuroinflammation was characterized by increased anxiety and impaired exploratory activity, while the old and animals with a single acute inflammation did not differ from the control group. However, both 18-month-old mice and those with chronic and acute LPS administration differed from the control by a reduced number of grooming acts. In the "Novel Object Recognition" test, animals with induced chronic neuroinflammation showed a tendency to invert the response to novelty, and also showed a significant decrease in spatial hippocampal-dependent memory in «Barnes Maze».

Thus, chronic systemic inflammation affects both basic activity and anxiety, as well as hippocampal-dependent forms of memory. At the same time, in young animals that underwent acute inflammation, a long-term recovery of cognitive functions and basic activity was observed.

"MOLECULAR MECHANISMS OF AGING" WORKSHOP

The workshop "Molecular Mechanisms of Aging" is organized to discuss advances in various fields of research related to the study of the molecular mechanisms of aging and age-related diseases. One of the topical issues is the relationship between healthy aging and age-related pathologies – cardiovascular, neurodegenerative, oncological and others. At the same time, even in the absence of age-related diseases, the unfavorable changes progressively accumulate in the elderly, also calling for elucidation and identification of the possible preventive and theurapevtic molecular targets. Given the amount of produced multi-omics data in the field and the complexity of aging itself, the progress is hardly possible without developing advanced methods of data analysis, including machine learning and AI.

The workshop is envisaged as an interdisciplinary forum bringing together experts from different backgrounds to exchange opinions and ideas, building collaborations that would lead to improving our understanding and potentially control of the aging process.

SEX-SPECIFIC AGE-RELATED DNA METHYLATION CHANGES

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Aims

During aging, DNA methylation patterns are remodeled [1]. Increased epigenetic age is associated with age-related diseases (cardiovascular diseases, neurodegenerative conditions, cancer [2]), while decreased epigenetic age is associated with healthy aging and longevity [3].

According to the WHO [4], life expectancy at birth in 2016 was 74.2 years for women and 69.8 years for men, and this gender gap in life expectancy is observed throughout the world [5]. At the same time, epidemiological data show that women live longer than men, but their quality of life deteriorates in old age [6].

A study of sex differences in changes in whole blood DNA methylation with aging was performed. In particular, we focused on: 1) age-related changes in the level of DNA methylation; 2) age-related increase in the variability of DNA methylation.

Methods

From the Gene Expression Omnibus (GEO) [7] repository, the 3 largest whole blood methylation datasets were selected: GSE40279 [8], GSE87571 [9] and GSE55763 [10]. In addition, a fourth dataset was analyzed, which is part of the EPIC Italy study [11]. Samples were excluded from each dataset according to [12], 327905 samples take part in the analysis.

To find CpG sites with differences in DNA methylation between the two sexes during aging (saDMPs), the following analysis was performed: 1) Meta-analysis of 4 datasets to identify samples with sex-specific DNA methylation patterns (sDMPs). 2) Meta-analysis of 4 datasets to identify samples with age-related DNA methylation patterns (aDMPs). 3) Only samples with a consistent trend were considered in all 4 datasets (for sDMP: hypermethylated or hypomethylated in males versus females; for aDMP: hypermethylated or hypomethylated with age). 4) The intersection of the sDMP and aDMP lists yielded a saDMP list of 16526 samples.

To find samples having sex differences in age-related methylation variability (saVMPs), the following analysis was performed: 1) First, counts of CD8T cells, CD4T cells, NK cells, B cells, and granulocytes in each set were regressed out. 2) To check heteroscedasticity by age, the Breusch-Pagan method was applied for men

and women separately in each dataset. 3) Heteroscedasticity p-values were analyzed using a sample-weighted meta-analysis separately for men and women. 4) Three possible scenarios of sex differences in age-related methylation variability were identified: a) heteroscedasticity in women and homoscedasticity in men; b) homoscedasticity in women and heteroscedasticity in men; c) heteroscedasticity in both women and men, with opposite directions of variability change (increases in women and decreases in men, or decreases in women and increases in men).

Results

A meta-analysis of 4 large whole blood datasets for sDMPs was performed, and 38100 sDMPs were found, 53% of which were hypermethylated in women compared to men. 87581 aDMPs were found, 52% of which were hypermethylated with age. The intersection between the sDMP and aDMP lists yielded 16526 samples that are related to sex and age at the same time (saDMP). Most of the hypomethylated with age saDMPs are more methylated in men than in women, while most hypermethylated with age saDMPs are more methylated in women than in men.

809 and 12178 saVMPs were found specific for women and men, respectively. All female-specific saVMPs showed increased variability with age, and for only 5 of 12,178 male-specific samples, saVMP variability decreased with age. There were no samples with opposite tendencies in men and women.

Conclusions

We describe the algorithm to find probes with sex-specific age-related differences in DNA methylation in whole blood. Men and women were compared for age-related changes in hyper- or hypomethylation and also for such type of epigenetic remodeling as variability, which can affect aging and contribute to an increase in life expectancy. The analysis was performed on 4 different datasets, including subjects from different geographic regions (USA, Sweden, Italy, UK) and belonging to different ethnic groups (Europeans, Hispanics). A meta-analysis of these datasets allowed to separate the influence of gender from the influence of genetic background and socio-cultural aspects. The results suggest that most of the CpG sites with sex-specific DNA methylation patterns are also modulated during aging, and sex may influence some aspects of age-related epigenetic remodeling, such as increased variability in DNA methylation.

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BIOCHEMICAL AND IMMUNOLOGICAL MARKERS OF ACCELERATED AGING IN PATIENTS WITH END-STAGE RENAL DISEASE

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Aims

Accelerated aging is a process associated with the accumulation of harmful changes in the body and an increased risk of disease and death. Despite advances in the treatment of chronic kidney disease (CKD) and optimization of the end-stage hemodialysis process, morbidity and mortality in this group of people remain constantly high [1]. Identification of markers of accelerated aging and a detailed understanding the mechanisms of the pathogenesis of CKD will allow identify possible interventions to improve the quality of life of patients. The aim of this work was to identify markers of accelerated aging in patients with end-stage renal disease.

Methods

The study involved 163 people living in the Nizhny Novgorod region. The group of patients with end-stage of CKD included 77 people aged 28 to 89 years with various hemodialysis experiences. The control group was represented by conditionally healthy volunteers aged 29 to 88 years without chronic diseases in the acute phase. The phenotypic age was determined using the PhenoAge model [2], which is based on 9 blood parameters. Determination of epigenetic age was carried out by genome-wide analysis methylation on Illumina EPIC BeadChip using the Horvath calculator [3]. To identify factors associated with accelerated aging, we determined the level of four biomarkers: GDF15, FGF21, FGF23 and Klotho in blood plasma using enzyme-linked immunosorbent assay (ELISA). To characterize the immunological profile, multiplex analysis of 47 cytokines was performed using Milliplex MAP systems.

Results

The results of the study of phenotypic and epigenetic age showed significant differences ($p < 0.05$) between two groups of subject. In patients on hemodialysis, there is a significant age-related acceleration compared with the control group. According to the results of multiplex analysis of cytokines, 18 indicators were identified that significantly differed in the studied groups, while in addition to classical markers of inflammation, atypical biomarkers were identified, which are probably involved in the pathogenesis of accelerated aging. Also, there were revealed significant differences ($p < 0.05$) in the level of FGF21, FGF23 and GDF15 in the blood plasma of patients compared with the control group.

Conclusions

Our results show age-related acceleration against the background of chronic inflammation and changes in biochemical markers of homeostasis. The factors listed above are involved in the formation of the accelerated aging phenotype characteristic of patients with end-stage renal disease.

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BIOLOGICAL AGE PREDICTION BASED ON COGNITIVE QUANTIFIERS

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Aims of the study

As people get older impairments in memory and processing can arise due to development of neurodegenerative disorders. Decline in cognitive abilities deteriorates the quality of life, reduces productivity of individual in the professional and social life. An easily scalable approach of cognitive state tracking can help in early diagnosis of emerging diseases. There are many well-established different approaches to assess cognitive abilities. However, few studies investigate imprints of cognitive aging processes in blood and epigenetic profile. Thus, the aim of this work was to analyze possibility of biological age estimation from the individual cognitive indices.

Methods

Dataset consists of one hundred participants (age 19-78 years). The participants were tested by three cognitive tests [1-2] and a blood sample were received from them. The participants were asked to distinguish the image stimuli of the background by changing hue of stimuli, check correctness of arithmetic expressions, and mark letter stimuli in case it wasn't mirrored. Actions of subjects and corresponding durations of sensorimotor reaction and motor reaction were recorded. Based on those cognitive indices were computed sample statistics that were used as input dataset for machine learning algorithms. The second part of dataset are biological and epigenetic ages that estimated on the obtained blood samples according to papers [3-4].

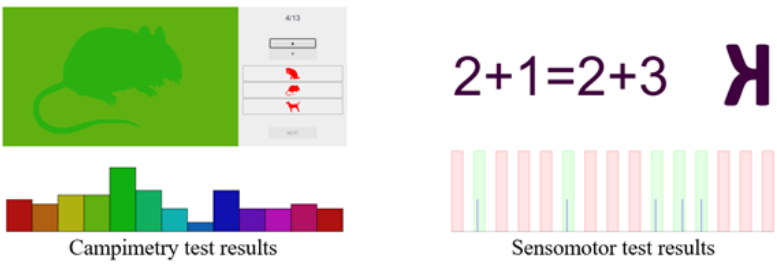

Fig.1. The visual stimuli presented in the campimetry test and sensorimotor test

Standard machine learning techniques from the scikit-learn package [5] were used for solving nonlinear regression problem of prediction age-characteristic based on cognitive quantifiers. Quality of fit and hyperparameters were optimized by the cross-validation algorithm with the explained variance as a loss function. Optimal models were selected for each age-characteristic: chronological age, DNAmAge and Levine's age

model. As nonlinear models were applied Support Vector Machine with radial basis function, k Nearest Neighbors method and Artificial Neural Networks.

Results

We compared performance of three considered models over epigenetic, chronological and phenotypic age. The minimum of median absolute error was obtained using support vector machine algorithm on epigenetic age and average MedAE over cross-validation equal to 4.66 years. Prediction of chronological age from cognitive quantifiers are less accurate than for epigenetic age. However, quality of phenotypic age prediction that estimated on blood biochemistry are quite good and median absolute error is 5.17 years. The best performer model for both cases is a support vector machine.

Conclusions

In our work, we find out that difference between epigenetic age and chronological age can be partly explained by changes in cognitive abilities of individual. The epigenetic profile that corresponds to age-related CpG sites according to Horvath clock through its linear combination is shown to be associated with cognitive indices such as time of distinguishing stimuli from the background, duration of sensorimotor reaction and sensomotor reaction during the arithmetic test and mirrored letters test. The phenotypic age constructed on the blood biochemistry also reflects cognitive-related changes that associated with aging processes.

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AGE-RELATED CHANGES IN THE BEHAVIOR AND EXPRESSION OF BRAIN-DERIVED NEUROTROPHIC FACTOR AND ITS RECEPTORS IN ZBTB33 KNOCKOUT MICE.

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The aging process is an essential part of all organisms' life. However, the neurobiological processes associated with age-related changes are still unknown. Aging is frequently associated with cognitive decline and affective disorders in human induced by neurodegenerative process in the brain, and usually accompanied by the disturbance of processing or production of brain-derived neurotrophic factor BDNF in the hippocampus. BDNF promotes positive effects on neuroplasticity-related processes, while its precursor protein proBDNF activates

apoptosis-related signaling pathways and may facilitate long-term depression in the hippocampus. BDNF and proBDNF exert their influence through the TrkB and p75 receptors, respectively. Nowadays it is well known that aging is also associated with changes in the DNA methylation. The transcription factor Kaiso encoded by *Zbtb33* gene recognizes methylated cytosine residues and using protein complexes regulates the transcription of genes in the cell. However, the role of age dynamics on the Kaiso transcriptional factor has not been studied yet.

The aim of this study was to evaluate age-related changes in the behavior and expression of BDNF and its receptors in hippocampus of *Zbtb33* knockout mice.

Methods

The experiments were carried out on 6-, 12 - and 18-month-old *Zbtb33* knockout female mice. The behavior of animals was studied in the open field, dark-light box and tail suspension tests. The expression of genes encoding BDNF, TrkB and p75 receptors in the hippocampus were assayed by real-time PCR and the protein levels of proBDNF, BDNF, TrkB and p75 were evaluated by Western blot analysis. The data were analyzed using one-way ANOVA. Statistical significance was set at $p<0.05$.

Results

We found that aging in these animals is associated with decrease in distance traveled ($p<0.01$) and number of rearings ($p<0.001$) in the open field test. While there was no effect of age-related changes on the behavior of *Zbtb33* knockout mice in the dark –light box and tail suspension tests. Moreover, in the hippocampus, there were no age-related changes in the mRNA levels of the genes encoding BDNF, TrkB and p75 in knockout mice. At the same time, the 18-month-old *Zbtb33* mice demonstrate an increase in the level of pro-apoptotic protein pro-BDNF ($p<0.05$) in comparison to those of 6- and 12 -month old mice, however there were no changes in the level of BDNF, p75, and TrkB proteins in the *Zbtb33* knockout mice with age.

Conclusion

Thus, for the first time it was shown that aged *Zbtb33* gene knockout mice show a decrease in locomotion and exploration activity, as well as an increase in the level of the pro-BDNF protein in the hippocampus, which may indicate possible apoptotic processes in the brain.

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ACCELERATED AGING WITH CHRONIC KIDNEY DISEASE: EPIGENETICS AND IMMUNOLOGY

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Aims

Chronic kidney disease (CKD), which leads to end-stage renal disease (ESRD), is a major public health problem as more and more people around the world suffer from it [1]. Many people with ESRD require renal replacement therapy, such as dialysis or a kidney transplant. CKD leads to a decrease in the quality of patients' life and is associated with an increased risk of premature death. One of the critically important issues is to develop biomarkers, which allow to identifying people with increased risk of CKD developing. This could potentially allow using targeted therapy to delay the onset or progression of CKD. Kidney function, measured by estimated glomerular filtration rate (eGFR) [2], decreases with age. Identifying patients with an excessive rate of deterioration is a critically important issue [3].

Epigenetic modifications control gene expression without changing the DNA sequence. DNA methylation (DNAm) is a main epigenetic feature and a key regulator of transcription. Several previously published studies have identified differentially methylated CpG sites associated with CKD or its progression [4]. These works used

a cross-sectional design (comparison Illumina 27k and 450k results) and different statistical approaches to determine the list of CpG sites significantly associated with the disease.

In this work, we introduce Illumina Infinium MethylationEPIC BeadChip microarray data from the 76 subjects with ESRD (undergoing dialysis) and 83 control subjects from the Russian population. Both groups have a wide range of ages, so our idea is to study age acceleration in a group with the disease in terms of the most popular estimators of epigenetic and biological age [5-8]. We also consider the immunological biomarkers for these subjects.

We aim to analyze age-acceleration in a group of subjects with ESRD in terms of the most popular biological clock, identify immunological biomarkers associated with aging and ESRD, and build on their basis a new type of chronological age estimator (clock).

Methods

Dataset consists of 159 subjects (76 with ESRD and 83 controls) with the age range from 24 to 88. For these subjects, we obtain DNA methylation data and immunology profiles with Illumina EPIC BeadChip and Multiplex Assay Kit, respectively.

To identify the increased age-acceleration ratio in the ESRD group, we firstly obtain age estimation values from different types of clocks [5-8], then build a linear regression model only on controls and calculate residuals from this model. Mann-Whitney U test was applied to residuals to analyze the statistically significant difference of age acceleration between controls and ESRD. To build a new age estimator (clocks), we applied the Elastic Net regression model to 46 Multiplex biomarkers to select variables for our clocks. To choose the best model parameters we perform 5-fold cross-validation on the parameters grid. To find the most associated with ESRD immunology biomarkers, we performed the Mann-Whitney U test, where biomarkers values were taken as continuous variable and group (control or ESRD) were taken as a categorical variable. To analyze the correlation between the biomarkers and different estimations of age we used Pearson correlation.

Results

Our results demonstrate that the majority of age estimators (clocks) show statistically significant age acceleration in the ESRD group. The proposed in this works clock also indicates significant age acceleration in the ESRD group and demonstrates a greater sensitivity in assessing the adaptive potential of an organism due to the higher blood parameters variation in comparison with the epigenetic changes. We also found that 18 of 46 immunology biomarkers are associated with the disease, and 11 are associated with different types of age estimators. For the top-ranked biomarkers, we obtain the biological interpretation and connection with ESRD.

Conclusions

In our work, we analyze epigenetic and immunology biomarkers from the 159 subjects to find the age acceleration footprints of chronic kidney disease. We performed statistical analysis of immunological biomarkers and highlighted among them those that are most associated with ESRD, as well as age. Using machine learning methods, we constructed immunological clocks, which estimate chronological and biological age using the optimal subset of biomarkers.

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AUTHOR INDEX

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