THIRD SCIENTIFIC CONFERENCE

"NEUROSCIENCES – FROM THEORY TO EXPERIMENT AND PRACTICE"

23-25 October 2020, Bachinovo, Bulgaria

ABSTRACT BOOK

Supported by the Institute of Neurobiology, South-West University and the National Research Program "BioActiveMed"

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SCIENTIFIC PROGRAM

23-25 October 2020, Bachinovo, Bulgaria

Friday, October 23th, 2020

20:00 – 20:45	**Registration**

Saturday, October 24th, 2020

9:15 – 9.30	**Welcome Words:** **Rector of the South-West University Prof. Borislav Yurukov** **Chairperson of the Organizing Committee Prof. Reni Kalfin**
	SESSION 1. NEUROBIOLOGY **Chair Prof. L. Tancheva**
9:30 – 9:45	**P. Dolashka, L. Velkova, A. Dolashki, V. Atanasov, L. Tancheva, M. Lazarova, L. Alova, W. Voelter "Proteomics analysis in Alzheimer's disease"**
9.45 – 10.05	**V. Atanasov, L. Velkova, L. Tancheva, A. Dolashki, R. Kalfin, P. Dolashka "Effect of *Helix aspersa* extract on hippocampal and cortex protein profile in scopolamine rat model of Alzheimer's disease"**
10.05 -10:25	**L. Tancheva, M. Lazarova, P. Dolashka, A. Dolashki, L. Velkova, M. Stefanova, D. Uzunova, P. Gavrilova, A. Alexandrova, E. Tsvetanova, Y. Hodzev, R. Kalfin "How fresh extract of snail (*Helix aspersa*) improves memory capacity of dement experimental rats"**
10:25 – 10:45	**E. Dzhambazova, B. Assenov, P. Pakataridis, D. Pechlivanova, P. Peneva, S. Georgieva, P. Todorov "Effects of VV-hemorphin-7 analogues on nociception in mice"**
10:45 – 11:15	**COFFEE BREAK**

11:15 – 11:35	**D. Pechlivanova, B. Assenov, I. Chan, H. Angelova, E. Dzhambazova "Effects of kyotorphin on motivation, habituation and working memory"**
11:35 – 11:55	**T. Pajpanova, T. Dzimbova "Unnatural amino acids - improve affinity, stability and potency of opioid peptides?"**
	<u>SESSION 2.</u> BEHAVIORAL AND COGNITIVE NEUROSCIENCES **Chair Prof. V. Kolev**
12:00 – 12:20	**I. Vankov "Solving the binding problem in memory and vision"**
12:20 – 12:40	**V. Kolev, A. Raffone, J. Yordanova "Connectivity patterns in contemplative states"**
12:40 – 13:00	**Ts. Totev, N. Bocheva, S. Stefanov, M. Mihaylova "The advantage to use noise and how to apply it"**

13:00 – 14:00 LUNCH BREAK

15:00 – 16:00 POSTER SESSION "A" Neurobiology

16:30 – 17:30 POSTER SESSION "B" Behavioral and Cognitive Neurosciences

20:00 – 22:30 GALA DINNER AND YOUNG SCIENTISTS AWARDS

Sunday, October 25th, 2020

11:00 FAREWELL

POSTER SESSION "A" NEUROBIOLOGY

1. M. Lazarova, D. Tsekova, L. Tancheva, K. Kirilov, D. Uzunova, L. Vezenkov, E. Tsvetanova, A. Alexandrova, A. Georgieva, P. Gavrilova, S. Dragomanova, M. Papazova, R. Kalfin "New peptides derivatives of Galantamine with potential to be acetylcholine esterase inhibitory and antioxidant agents"

2. P. Petkova-Kirova, M. Lazarova, D. Tsekova, D. Uzunova, L. Vezenkov, E. Tsvetanova, A. Alexandrova, P. Gavrilova, Y. Hasanova, R. Kalfin, L. Tancheva "Effects of new galantamine derivatives in a scopolamine model of dementsia"

3. S. Miteva, S. Dragomanova, F. Nicolleti, M. Lazarova, A. Solak, R. Kalfin, D. Yarkov, R. Nikolov, L. Tancheva "Neurotoxic mechanisms of SARS-CoV-2"

4. M. Lazarova, P. Kirova, D. Uzunova, Y. Hassanova, P. Gavrilova, A. Popatanasov, C. Staykov, A. Solak, R. Kalfin, L. Tancheva "Effect of Alfa Lipoic Acid on behavioral and biochemical parameters of subchronic heavy metals intoxication of rats"

5. D. Uzunova, Y. Hassanova, P. Gavrilova, M. Lazarova, P. Kirova, A. Popatanasov, A. Alexandrova, E. Tzvetanova, M. Stefanova, A. Solak, J. Karaivanova, R. Kalfin, L. Tancheva "Modulatory effect of Zeolite on acetylcholine esterase activity in rats with subacute heavy metals intoxication"

6. E. Tsvetanova, A. Alexandrova, A. Georgieva, M. Lazarova, L. Tancheva, D. Uzunova, P. Gavrilova, A. Dolashki, L. Velkova, R. Kalfin, L. Tancheva, P. Dolashka "Effect of snail extract from Helix aspersa on brain redox status in scopolamine-induced dementia"

7. L. Velkova, A. Dolashki, V. Atanasov, L. Tancheva, M. Lazarova, L. Alova, W. Voelter, P. Dolashka "Analyses of hippocampus extracts from experimental animal model (rat) and assessment of neuroprotective effect of mucus extract from garden snail *Helix aspersa*"

8. A. Daskalova, L. Velkova, D. Kaynarov, A. Dolashki, V. Petrova, W. Voelter, P. Dolashka "Saccharomyces cerevisiae under oxidative stress as a model for the study of the mechanisms of neurodegenerative diseases"

9. H. Staykov, R. Nikolov, L. Tancheva "Pharmacological approaches in the treatment of memory impairment"

10. A. Ivanov, D. Atanasova, N. Lazarov "Expression of NGF, BDNF, and NT-3 in the spinal trigeminal nucleus in rats"

11. D. Atanasova, I. Maslarski, N. Dimitrov, A. Ivanov, N. Lazarov "Study of neurotrophic nature of the cell population in the carotid body of spontaneously hypertensive rats"

12. V. Karabelyov, V. Stoyanova, M. Kondeva-Burdina "In vitro effects of newly synthesized 1,3,4-oxadiazole derivatives, administered alone, on isolated rat brain synaptosomes"

13. B. Yakimova, P. Mateeva, P. Kardaleva, I. Stoineva, P. Todorova, R. Zamfirova "In vitro studies on Angiotensin-I converting enzyme (ACE) inhibitory activity of short synthetic peptides"

14. N. Kircheva, S. Dobrev, B. Yakimova, I. Stoineva, S. Angelova "Molecular Insights into the Interaction of Angiotensin I-Converting Enzyme (ACE) Inhibitors and HExxH Motif"

15. T. Dzimbova, F. Spundzhi, P. Milanov "Application of molecular docking for prediction the activity of potential μ-opioid receptor ligands"

POSTER SESSION "B" BEHAVIORAL AND COGNITIVE NEUROSCIENCES

1. N. Ivanova, Z. Nenchovska, R. Mitreva, M. Atanasova, J. Tchekalarova "Beneficial impact of the novel melatoninegric compound piromelatine on depression and hypothalamic-pituitary-adrenal axis activity in prenatally stress male offspring"

2. V. Karabeliov, B. Petrov, V. Angelova, N. Ivanova, T. Stoyanova, Z. Nenochovska, R. Tzoneva, P. Gateva, J. Tchekalarova "Synthesis, antidepressant and anxiolytic effects of novel melatonin analogues in rodent models"

3. N. Ivanova, Z. Nenchovska, R. Mitreva, M. Atanasova, J. Tchekalarova "Effects of piromelatine on memory deficits and corticosteroid receptors alteration induced by prenatal stress in male offspring"

4. V. Uzunova, A. Tsiapla, O. Kalogirou, M. Angelakeris, J. Tchekalarova, R. Tzoneva "Anti-oxidant activity of magnetic nanoparticles and magnetic field in rodents"

5. P. Nanova, V. Kolev, J. Yordanova "ERP correlates of age-related gender differences in auditory selective attention"

6. J. Yordanova, V. Giannouli, L. Lyamova, Y. Tankovski, R. Kirov, V. Kolev "Processing strategies in dual-tasking: Aging-related similarities and differences"

7. J. Yordanova, R. Kirov, K. Beshkov, P. Nanova, V. Kolev "Effects of aging on motor theta networks"

8. K. Beshkov, P. Tiesinga "Topological characteristics of neural manifolds"

9. M. Staneva, V. Grigorova "Evaluation of visual-motor integration in the performance of a decision-making task after the application of semantic priming for a for wide attention focus"

10. K. Racheva, Ts. Totev, E. Natchev, N. Bocheva, R. Beirne, M. Zlatkova "Assessment of colour discrimination in hypothyroidism after drug treatment using FM 100 test"

11. M. Stefanova, N. Bocheva, B. Genova, A. Hristov, R. Kraleva, V. Kralev "Age-related changes in eye movements' characteristics in decision-making and classification tasks"

12. I. Hristov, S. Stefanov, N. Bocheva, M. Stefanova, K. Racheva, K. Shtereva, M. Mihaylova "The effect of external noise on the motion direction sensitivity in children and adolescents with Developmental Dyslexia"

13. B. Genova, N. Bocheva, M. Stefanova, A. Hristov "Effect of age in single- and multi-cue classification tasks"

ORAL PRESENTATIONS

PROTEOMICS ANALYSIS IN ALZHEIMER'S DISEASE

P. Dolashka[1], L. Velkova[1], A. Dolashki[1], V. Atanasov[1], L. Tancheva[2], M. Lazarova[2], L. Alova[2], W. Voelter[3]

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Abstract: Alzheimer's disease (AD) is the most common form of dementia. It is the sixth leading cause of death, and affects nearly 30 million people worldwide. Scopolamine and streptozotocin are widely utilized in chemically-induced dementia animal models to mimic specific pathophysiological pathways thought to underline AD. To the best of our knowledge, there is no report describing proteome analysis on scopolamine or streptozotocin AD animal models. Therefore, we conducted a comparative proteome analysis on CSF isolated from rats with chemically-induced dementia with the purpose of identifying protein biomarkers. Rodents were divided into three groups: rats with scopolamine-induced dementia, rats with streptozotocin-induced dementia and healthy controls. Proteins and peptides were separated from the isolated CSF into four fractions. Two low molecular peptide fractions, with mass below 3kDa, and another with mass ranging from 3 to 10 kDa were analyzed by mass spectrometry, while two other protein fractions, with mass between 10 and 50 kDa, and with mass higher than 50 kDa, were characterized by 2D-PAGE and the results were compared.

Using MASCOT Peptide Mass Fingerprint the hippocampal proteins have been identified and compared. The mucus extract from *H. aspersa* exerted antioxidant and neuromodulatory activity - it increased the content of dopamine and noradrenaline in the hippocampus, corrected oxidative damages and totally reversed the effect of scopolamine.

Keywords: Alzheimer’s disease, hemocyanin, proteome analysis, CSF, scopolamine, streptozotocin

Acknowledgements: This work was supported by the National Research Programme “Innovative Low-Toxic Bioactive Systems for Precision Medicine (BioActiveMed)” approved by DCM № 658/14.09.2018 funded by the Bulgarian Ministry of Education and Science, Bulgaria

EFFECT OF HELIX ASPERSA SNAIL EXTRACT ON HIPPOCAMPAL AND CORTEX PROTEIN PROFILE IN SCOPOLAMINE RAT MODEL OF ALZHEIMER'S DISEASE

V. Atanasov[1], L. Velkova[1], L. Tancheva[2], A. Dolashki[1], R. Kalfin[2], P. Dolashka[1]

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Abstract: Alzheimer's disease (AD) is a chronic neurodegenerative disease that progresses slowly and gradually worsens over time and is the cause of 60–70% of cases of dementia. Along with Parkinson's disease, they are the most common neurodegenerative diseases among the elderly population of great social significance. Usually the life expectancy after diagnosis is 3-9 years. AD is characterized by loss of neurons and synapses in the cerebral cortex and some subcortical areas. This loss leads to large-scale atrophy of the affected regions, including degeneration in the temporal and parietal lobes, as well as parts of the frontal cortex.The scopolamine is frequently used agent for induction of Alzheimer in experimental animals. We used scopolamine model for assessment of potential neuroprotective effect of extract from garden snail *Helix aspersa* on neurodegenerative processes *in vivo*. Male sexually mature experimental rats were used. They were divided into three groups: a control group of healthy rats, a scopolamine group (treated with scopolamine) and an experimental group treated with scopolamine and snail extract together. Two major memory-related brain structures (hippocampus and prefrontal cortex) are isolated. The obtained proteins were separated by SDS – PAGE and analyzed with MALDI-MS. Using MASCOT Peptide Mass Fingerprint and Uniprot Protein Database the cortex and hippocampal proteins have been identified and compared. We observed a decrease in the expression of synapsin, tubulin and pyruvate kinase in the scopolamine group of rats compared to the control group and an increase in protein expression in the animals treated with scopolamine and snail extract together.

Keywords: Alzheimer's desease (AD), scopolamine, snail extract, neuroprotective effect, rat brain, rat brain proteins

Acknowledgements: This work was supported by the National Research Programme "Innovative Low-Toxic Bioactive Systems for Precision Medicine (BioActiveMed)" approved by DCM № 658/14.09.2018 funded by the Bulgarian Ministry of Education and Science, Bulgaria

HOW FRESH EXTRACT OF SNAIL (HELIX ASPERSA) IMPROVES MEMORY IN RATS WITH EXPERIMENTAL DEMENTIA

L. Tancheva[1], M. Lazarova[1], P. Dolashka[2], A. Dolashki[2], L. Velkova[2], M. Stefanova, D. Uzunova, P. Gavrilova, A. Alexandrova[1,3], E. Tsvetanova[1], R. Kalfin[1]

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There are many reports about preventive and therapeutic effect of Snail extract (SE) against some diseases because of its rich biological activities (antioxidant, anti-inflammatory, membrane stabilizing etc.). But there are no data in the literature about its effect on the neurodegenerative disorders.

The aim of the current study is to clarify some main mechanisms involved in established memory improving effect of fresh mucus SE using experimental model of dementia in rats produced by Scopolamine treatment (2 mg/kg, ip, 11 days).

We found that SE significantly compensated the memory deficits, observed in rats with experimental dementia, and had a positive effect both on short- and long- term memory processes. The learning and memory capacity in dement rats was significantly improved and almost reached levels of healthy controls. Memory protective effect of SE was accompanied by significant inhibition of acetylcholine esterase activity in the hippocampus, but not in the cortex. SE exerted also neuromodulatory activity - it increased the content of dopamine and noradrenaline in the cortex as well as in the hippocampus, and totally reversed the scopolamine action. Oxidative damages observed in brains of dement rats were significantly corrected by SE administration. Lipid peroxidation, total glutathione, activities of antioxidant enzymes catalase and glutathione peroxidase assesed in brain structures related to the memory process were normalized after SE treatment.

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Keywords: Snail extract, Dementia, Memory, Alzheimer’s disease

EFFECTS OF VV-HEMORPHIN-7 ANALOGUES ON NOCICEPTION IN MICE

E. Dzhambazova[1], D. Pechlivanova[2,1], B. Assenov[1,2], P. Pakataridis[1], P. Peneva[3], S. Georgieva[4], P. Todorov[3]

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The development of new groups of analgesics and anti-inflammatory drugs is constantly of interest to clinical practice. Endogenous short-chain peptides and their analogs are one of the progressive areas of research. Hemorphins are such type peptides, which have affinity to both opioid receptors and insulin-regulated aminopeptidase. We hypothesize that the synthesis of hemorphin analogs with a specific Arg-Gly-Asp (RGD) sequence will improve localization and sustain the potency of the peptide-induced antinociception.

This study aimed to establish the antinociceptive profile of VV- hemorphin-7 (VV-H-7) and its newly synthetized analogs modified at the N- and C-terminus – RGD1 and RGD2. We have used the formalin test in mice which is suitable for studying acute and inflammatory nociception. Three doses of each peptide (2.5, 5, and 10 μg/mouse) were injected intracerebroventricularly before the irritant application.

All studied peptides exerted structural- and dose-dependent antinociceptive effects in the formalin test in mice. RGD1 showed a lower effective dose in the acute phase and a preserved dose-dependent antinociceptive profile in inflammatory pain compared to the precursor peptide. RGD2 showed an antinociceptive effect at lower doses compared to VV-H-7, with no pronounced dose-dependence in the inflammatory phase of the formalin test.

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EFFECTS OF KYOTORPHIN ON MOTIVATION, HABITUATION AND WORKING MEMORY

D. Pechlivanova[1,2*], B. Assenov[2,1], I. Chan[2], H. Angelova[1], E. Dzhambazova[2]

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The endogenous dipeptide kyotorphin (KTP) was found in brain structures that take a part in the processing of pain information, the control of emotions, and memory formation. Additionaly KTP has a mild neuroprotective effect against deleterious effects of brain hypoperfusion and Alzheimer's disease. We aimed to study the effects of antinociceptive doses of KTP on the motivational behavior, memory, and levels of the carbonylated proteins in healthy Wistar rats.
We have used paw-pressure test for nociception, open field test for exploration and habituation to new environment, elevated plus maze test for anxiety-like behavior, and novel object recognition test for working memory. Carbonylated protein assay was used for measurement of the impaired proteins.
KTP exerted an antinociceptive effect at doses of 25, 50 and 100 μg/rat, ICV, but not after chronic administration. Only 100 μg KTP was able to induce anxiolytic and motor inhibiting effects. None of the doses used have shown effects on the recognition memory or the level of the carbonylated protein. Our results showed that KTP realized its antinociceptive effect without substantial side effects on the basic behavioral parameters related to the exploration, motivation, memory formation, and blood and brain carbonylated protein in healthy rats.

Acknowledgments: Supported by Grant 80-10-1/2020, Sofia University.

UNNATURAL AMINO ACIDS: IMPROVE AFFINITY, STABILITY AND POTENCY OF OPIOID PEPTIDES ?

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[2]*South-West University "Neofit Rilski", Blagoevgrad*

Amino acids are a privileged class of building blocks in drug design. Synthesis of new unusual amino acids has always been in focus of our research for more than 20 years ago.

The numerous proposed examples of unnatural amino acids could include applications as: anti-cancer drugs; antibiotics that would be able to thwart bacterial resistance; drugs that inhibit the formation of amyloid aggregates such as those seen in Alzheimer's, Parkinson's and other diseases; radiopharmaceuticals and components of pharmaceuticals.

We have been focused also, on the roles of non-protein amino acids in modulating stability, potency, permeability and oral bioavailability of the peptides.
We are presenting the predicament faced in the peptide therapeutics and how non-proteinogenic amino acids incorporation can play a role in improving opioid peptide pharmacokinetic properties.

SOLVING THE BINDING PROBLEM IN MEMORY AND VISION

I. Vankov

Institute of Neurobiology, Bulgarian Academy of Sciences

Background: The binding problem has been a pivotal topic of discussion in psychology, neuroscience and artificial intelligence for decades. Generally, it concerns how distinct neural representations are combined to form new ones. The difficulty of binding neural representations is threefold. First, there is the problem of the superimposing simultaneously activated representations which can result in ambiguous states. The second manifestation of the binding problem occurs when more than one instance of the same concept (object, action) needs to be represented. Finally, there is the problem of variable binding - the ability to temporarily associate two representations which may have not been associated before.

There have been multiple proposals for solving the binding problem, but none of them has been accepted unanimously. In our view, one of the most promising lines of research is the idea of binding pools (Bowman & Wyble, 2007), which has been used to account for binding in attentional blink and visual working memory (Swan & Wyble, 2014). In this talk, we present a computational investigation which implements a binding pool in order to address the binding problem in an influential neural network model of immediate serial recall (Botvinick & Plaut, 2006).

Methods: A series of computer simulations with a neural network model comprising two components - an implementation of a binding pool and a replication of the Botvinick & Plaut (2006) model.

Results: We show the new two-component model is capable of storing novel combinations of items and temporal positions, while still accounting for key benchmark phenomena.

Conclusions: Our investigation demonstrates how implementing a binding pool can address the problem of generalization across untrained temporal positions in neural network models of short-term memory.

Acknowledgement: Supported by the National Science Fund at the Ministry of Education and Science, Sofia, Bulgaria (project KP-06-N33/11).

CONNECTIVITY PATTERNS IN CONTEMPLATIVE STATES

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The major objective of the present study was to elucidate the neural grounds of contemplative states. Specifically, neuro-functional connectivity associated with different meditation practices was analyzed. For that aim, commonalities and differences in electroencephalographic patterns of spatial synchronization across three important meditation types were explored (focused attention, open monitoring, and loving kindness meditation). To ensure that the meditation states are reliably established, highly experienced meditators with years-long practice were studied. As a measure of neural coupling the imaginary part of EEG coherence was used. It was found that all meditation conditions displayed a common connectivity pattern characterized by increased connectivity of (a) broadly distributed delta networks, (b) left-hemispheric theta networks with a local integrating posterior focus, and (c) right-hemispheric alpha networks, with a local integrating parieto-occipital focus. Furthermore, each meditation state also expressed specific synchronization patterns differentially recruiting left- or right-lateralized beta networks. These observations provide original evidence that in addition to global patterns, frequency-specific inter-hemispheric asymmetry is one major feature of meditation, and that mental processes specific to each meditation type are also supported by lateralized networks from fast-frequency bands.

Acknowledgements: Supported by the National Science Fund at the Ministry of Education and Science, Sofia, Bulgaria (project KP-06-N33/11)

THE ADVANTAGE TO USE NOISE AND HOW TO APPLY IT

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Recently, the application of background visual noise is a widely used approach to broaden our understanding of visual information processing, The rationale behind this is the assumption that sensory processing is limited by both the external noise inherent in the environmental signals and by the internal noise in the neural system. Comparing sensitivity to stimulus characteristics with and without background noise allows separating the observer's ability from the observer's intrinsic noise.

Typically, the external noise used in visual perception studies is pixel noise i.e a type of noise where pixels with predetermined intensity and color, usually evenly distributed over the whole image, are added to it. However, in such a way the mean intensity or color is altered and this change might have a confounding effect on the subject's performance. We developed a method and software for a generation of pixel noise by pixel replacement. The procedure could be applied sequentially to any number of selected colors present in the image. Most importantly, the final image preserves the color histogram of the original image no matter how many times the procedure is applied.

Acknowledgements: This study was funded by grant DN15/6 from 2017 of the National Science Fund of Bulgaria.

POSTER SESSION “A” NEUROBIOLOGY

NEW PEPTIDE DERIVATIVES OF GALANTAMINE WITH POTENTIAL TO BE ACETYLCHOLINE ESTERASE INHIBITORY AND ANTIOXIDANT AGENTS

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Introduction: New Galantamine (Gal) derivatives (GalDs) were designed to be better acetylcholinesterase (AchE) inhibitory agents than Gal. **The aim:** To evaluate effect of GalDs (codes 34, 43, 44 and 46) on learning and memory processes, their AChE inhibitory and antioxidant activity *in vivo* in healthy mice.
Methods: Male ICR mice (18-20 g) were used. Experimental groups: control (0.1 ml saline / b.w., i.p) and tested groups received one of four GalDs (50 mg/kg, i.p) for 7 days. On the 1st hour and on the 8th day after daily treatment the animals were tested for changes in learning and memory performance, AChE activity and main oxidative stress parameters. **Results:** New GalDs and Gal itself did not impair memory performance in healthy mice after single and repeated treatment. GalD 43 showed better AChE inhibitory activity than Gal in healthy mice after repeated treatment and had no significant antioxidant activity. The AChE inhibitory effect of GalDs 34, 44 and 46 was commensurable with those of Gal as referent. GalDs 34, 44, 46 demonstrated possibility to modulate enzyme and GalD 46 non enzyme antioxidant defense system in brain cells. **Conclusion:** We consider that some of new GalDs deserve further development on animal neurodegenerative models as promising therapeutic agents.
Acknowledgements: Supported by Grant ДН-03-8/2016 from the National Science Fund, Bulgaria.

EFFECTS OF NEW GALANTAMINE DERIVATIVES IN A SCOPOLAMINE MODEL OF DEMENTIA

P. Petkova-Kirova[1], M. Lazarova[1], D. Tsekova[2], D. Uzunova[1], L. Vezenkov[2], E. Tsvetanova[1], M. Stefanova[1], A. Alexandrova[1], P. Gavrilova[1], Y. Hasanova[1], R. Kalfin[1], L. Tancheva[1]

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Alzheimer's disease (AD), a progressive neurodegenerative disorder, characterized by memory loss and cognitive functions decline, is the most common form of dementia. Except for deposition of intraneuronal neurofibrillary tangles and extracellular beta-amyloid (Aβ) aggregates, massive loss of cholinergic neurons and decreased acethylcholine levels, are among the most important features of the disease and, although in recent years, different strategies have been tried, cholinesterase inhibitors like galantamine (Gal), remain the backbone of pharmacological treatment of the disease. In the present study four newly synthesized, improved Gal derivatives (Gal34, Gal43, Gal44, Gal46) were evaluated for a beneficial effect in a scopolamine model of dementia in mice. Male ICR mice were divided into a control (saline treated), scopolamine (Sco, 1mg/kg), Sco+Gal (Sco, 1mg/kg+Gal, 1mg/kg), Sco+Gal34 (Sco, 1mg/kg+Gal34, 50mg/kg), Sco+Gal43 (Sco, 1mg/kg+Gal43, 50mg/kg), Sco+Gal44 (Sco, 1mg/kg+Gal44, 50mg/kg) and Sco+Gal46 (Sco, 1mg/kg+Gal46, 50mg/kg) group and the respective substances applied intraperitoneally for nine consecutive days. Behavioural tests such as the step-through inhibitory avoidance (ST), T-maze and the hole-board test were carried out to assess learning and memory performance as well as locomotion and exploratory activity in each group. Levels of oxidative stress were also estimated by measuring, in brain homogenates, biochemical parameters such as lipid peroxidation (LPO), level of total reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) activities. Results show that Gal 43, 44 and, in particular, Gal46 are especially effective in improving both short-term and long term memory as judged by the significantly restored ST latency times at the 1^{st} and 24^{th} hour and at the 10^{th} day. Such an effect is accompanied by a favorable decrease in the scopolamine-induced increase in LPO and an increase in the scopolamine-induced decrease in total GSH. SOD, CAT and GPx levels are also favorably increased, particularly in the case of Gal 43, the latter performing the best also in the T-maze test. Although Gal34 does not show behavioural effects (ST test) as convincing as those of the other three Gal derivatives, it demonstrates persuasive antioxidant and restorative capacities (LPO, GSH, SOD, GPx), making all four Gal derivatives (and especially Gal43 and Gal34) promising AD treatment agents and prompting their further studies.

NEUROTOXIC MECHANISMS OF SARS-COV-2

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SARS-CoV-2 neurotropism is based on its affinity to ACE2 receptor in endothelial cells and in brain [1] as well as its ability to bypass the receptor as an entry door and use the olfactory bulbs for its transport to CNS. There also is a third entry pathway – transportation within immunocompetent inflammatory cells. The neurological symptoms observed so far in COVID-19 can be divided into direct neurotoxic mechanisms caused by the virus to neurons and glia, and indirect neurotoxic mechanisms. **Direct mechanisms** are related to neuro-inflammation followed by compromising the blood brain barrier and homeostatic dysregulation. Damage to brain homeostasis could lead to ventilatory lung function impairment as well as exacerbation of the respiratory failure resulting in profound hypoxia. The combination of hypoxia with existent neuro-inflammation leads to damage in the hippocampal and cortical areas manifesting as the neuropsychiatric effects of the virus [2,3]. **Indirect neurotoxic mechanisms include** mostly cytokine storm, virus-induced hypoxia as well as thrombotic inflammatory events. **Virus-induced** hypoxia as pathogenetic mechanism leads to pulmonary complications and damage to gas exchange [4] with subsequent hypoxia and metabolic acidosis, causing vasodilation and edema of the brain. The condition is associated with a high risk of increased intracranial pressure and acute cerebrovascular accidents. The thrombotic-inflammatory nature of COVID-19 infection is confirmed by the complication ischemic stroke [5,6]. Potential major contribution to the thrombotic state in some patients that produce anti-Pl autoantibodies may provoke a secondary and eventually even catastrophic APS [7].

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EFFECT OF ALFA LIPOIC ACID ON BEHAVIORAL AND BIOCHEMICAL PARAMETERS OF SUBCHRONIC HEAVY METALS INTOXICATION OF RATS

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Introduction: It is well known that presence of heavy metals (HM) in the environment have a toxic effect on the central nervous system of mammals. There are evidences about the role of some HM in ethiopathogenesis of neurodegenerative disorders as AD and PD. The effects of some HM on the cholinergic function also have been reported in the literature.

Aim: Possible protective effect of alfa lipoic acid (ALA) on memory formation, motor performance and exploratory activity in rats after subchronic intoxication with the heavy metals was studied. Changes in acetylcholine esterase (AChE) activity in main brain structures related to memory were also assessed.

Methods: Male Wistar rats were treated subchronically with HM salts ($ZnCL_2$ and $Pb(CH3COO)_2$ and their combination) 100 mg/kg in drinking water for 30 days. Half of the animals received also ALA (50 mg/kg, i.p) for 30 days. Control group drunk clean water. On the 24h and 31 days after the first treatment some behavioral tests (passive avoidance, hole board and rotarod tests) were performed. AChE activity in brain homogenates from hippocampus, cortex and striatum was also determined (Elman et al. 1961).

Results: Subchronic postnatal intoxication with $Pb^{2+}$and Zn^{2+} worsen neuromuscular coordination and changed exploratory activity of treated rats, but did not impair significantly memory formation. HM intoxication decreased AChE activity in the brain of heavy metals-exposed rats, as indication for cholinergic synapses deficit, most pronounced in hippocampus and cortex. But the combination Pb+Zn increased it in the three brain structures.

On the 31st day after the first treatment, ALA treatment returned latency time of reaction (step through test) and exploratory activity (hole board test) near to control levels. ALA administration modulated AChE enzyme activity in cortex, hippocampus and striatum near to the levels of the controls.

Conclusion: Our results demonstrated the modulatory effect of ALA on AChE activity in studied brain structures. As a chelating agent ALA has protective effect against HM toxicity but the mechanisms remain unclear.

MODULATORY EFFECT OF ZEOLITE ON ACETYLCHOLINE ESTERASE ACTIVITY IN RATS WITH SUBCHRONIC HEAVY METALS INTOXICATION

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Zeolites are hydrated natural or synthetic microporous crystals with well-defined structures containing AlO4 and SiO4 tetrahedra. Zeolite use in medicine is a relatively recent subject of interest. Dietary zeolite supplementation reduces oxidative damage and plaque generation in the brain of an Alzheimer's disease mouse model. The substantial role of zeolite as a factor essentially reducing Pb, Zn and their combination bioaccumulation is established in some experiments. But how Zeolite affect s the cholinergic function changed by heavy metals (HM) exposure remains unclear.

AIM of this study was to assess the effect of Zeolite on Acetylcholin esterase activity in rats with subchronic HM intoxication by Pb, Zn and their combination

Methods: Male Wistar rats were treated subchronically with HM salts (ZnCL2 and Pb(CH3COO)2 and their combination) 100 mg/kg in drinking water for 30 days. Half of the animals received also 2% Zeolite for 30 days with their regular food. Control group drink clean water. On the 24th hour after the last HM salts intake and Zeolite respectively, three brain structrures cortex, hippocampus and striatum were isolated and the specific AChE activity was measured according Ellman's method (1961).

Results demonstrated that subchronic HM intoxication decreased AChE activity in the brain of heavy metals-exposed rats, indication for cholinergic synapses deficiency, most pronounced in hippocampus and cortex.

Everyday Zeolite administration normalized AChE activity in the cortex, changed by Zn and combination. In striatum only the combination of Pb and Zn salts and Zeolite significantly increase the AChE activity.

Conclusion

Our results demonstrated restoring effect of Zeolite on AChE activity- reduced by heavy metals subchronic administration in some brain structures. The mechanisms of detoxifying effect of Zeolite against HM toxicity deserve further studies.

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EFFECT OF SNAIL EXTRACT FROM *HELIX ASPERSA* ON BRAIN REDOX STATUS IN SCOPOLAMINE-INDUCED DEMENTIA

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Alzhaimer's type dementia is progressive neurodegenerative disease and its prevalence is between 10-30% in the population over 65 years of age and at this stage for there is no open treatment. Because oxidative stress is involved in neurodegeneration, selected antioxidants, metal chelators, or other compounds with natural origin that support the enzymatic and non-enzymatic defense mechanisms appear to be the obvious choice for treating these disorders. So the aim of our study was to evaluate the effect of snail extract from *Helix aspersa* on oxidative stress parameters lipid peroxidation and total glutathione in cortex and hippocampus in scopolamine-induced dementia. Male Wistar rats were treated i.p. with scopolamine (2mg/kg) for 11 days along with peroral administration of fresh water snail extract (0.5 mL/100 g). On the 12th day all groups underwent behavioral verification tests (Step-through) and after the animals were decapitated, the brains removed and processed for evaluation of parameters of oxidative stress: levels of lipid peroxidation (LP) and total glutathione (GSH). The results of behavioral test showed significant improving effect of snail extract on the learning and memory of dement animals. This was accompanied by reduction of increased by Scop levels of LP as well as partly increase in GSH in both structures.

Future directions are for the development of new drugs with reduced toxicity and preserved pharmacological activity, and studies examining the involvement of ROS and antioxidants in various neurodegenerative diseases may be crucial for the discovery of new and reliable therapies.

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ANALYSES OF HIPPOCAMPUS EXTRACTS FROM EXPERIMENTAL ANIMAL MODEL (RAT) AND ASSESSMENT OF NEUROPROTECTIVE EFFECT OF MUCUS EXTRACT FROM GARDEN SNAIL *HELIX ASPERSA*

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Alzheimer's disease (AD) is the most common neurodegenerative disorder causing dementia in the elderly. Alzheimer's disease is thought to be caused by the abnormal build-up of proteins in and around brain cells. Although it's not known exactly what causes this process to begin, scientists now know that it begins many years before symptoms appear. Recently, it is suggested that for the development of Alzheimer's disease is due to mainly β-amyloid peptides and neurofibrillary assemblies consisting of phosphorylated tau proteins are responsible for plaque formation.

Two extracts of hippocampus from experimental animal model (rat) in normal and scopolamine-induced neurodegenerative disorder (type AD), were isolated and analyzed by proteomic techniques, mass spectrometry (MALDI-TOF-TOF) and bioinformatics' analysis.

Additionally, the scopolamine model was used for assessment of potential neuroprotective effect of mucus extract from garden snail *Helix aspersa* on neurodegenerative processes in vivo. The obtained proteins were separated by SDS – PAGE and analyzed with MALDI-MS. Using MASCOT Peptide Mass Fingerprint the hippocampal proteins have been identified and compared. The mucus extract from *H. aspersa* exerted antioxidant and neuromodulatory activity - it increased the content of dopamine and noradrenaline in the hippocampus, corrected oxidative damages and totally reversed the effect of scopolamine.

Keywords: Scopolamine-induced neurodegenerative disorder (type AD); mucus extract from *Helix aspersa*, mass spectrometry, MALDI-MS, MASCOT.

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SACCHAROMYCES CEREVISIAE UNDER OXIDATIVE STRESS AS A MODEL FOR THE STUDY OF THE MECHANISMS OF NEURODEGENERATIVE DISEASES

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Imbalanced redox states as a result from immoderate production of reactive oxygen species or abnormality in the antioxidant system induce oxidative stress. Human organs, especially the brain is unprotected in the high presence of reactive oxygen species. Studies have demonstrated that oxidative stress has a key part in the pathophysiology of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Thanks to the determination of the genome sequence of the Saccharomyces cerevisiae, nowadays, it is widely spread to use S. cerevisiae as a model organism for biochemical and molecular researches.

The aim of that research is to determine enzymes responsible for the adaptation to oxidative stress in Log and stationary phase. Therefore, the yeast strain S. cerevisiae BY4741, was treated with oxidative and drug agents (hydrogen peroxide, menadion, zeocyn and ibuprofen) in both phases. Proteomic analysis, including SDS PAGE coupled with mass spectrometry was used to find such proteins.

Analysis of the results from MALDI-TOF/MS spectra through Mascot database-Fingerprint was used to elucidate the enzymes. Seven bands were found and corresponding proteins were proposed: Cytochrome c peroxidase, Glutathione S-Transferase Omega-like, NAPDH-dependent diflavin reductase, DNA replication fork-blocking protein, Putative aryl alcohol dehydrogenase, AP-1-like transcription factor YAP5, GTP-binding protein. A deeper investigation of the conserved mechanisms expressing entry into, survival in and exit from quiescence in higher eukaryotes will help understanding the mechanisms of neurodegenerative diseases.

Keywords: neurodegenerative diseases- Alzheimer's disease and Parkinson's disease, reactive oxygen species, oxidative stress, Saccharomyces cerevisiae, SDS PAGE, MALDI- TOF MS, enzyme

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PHARMACOLOGICAL APPROACHES IN THE TREATMENT OF MEMORY IMPAIRMENT

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Introduction: Unless one has hyperthymesia, he or she is bound to forget most of his or her daily experiences. For the majority of people, forgetfulness is a normal part of life. It can, however, also be a symptom of an underlying disorder. And drawing a line between what is normal and what is not can be hard. While a degree of memory problems, as well as a modest decline in other thinking skills, can be a common part of aging, fairly easy to cope with, people with memory impairment can find it hard to do everyday activities. Remembering new events becomes more difficult, and recalling one or more memories of the past may feel impossible. The memory impairment may last for a short time and then resolve. Or, it may not go away, and, depending on the cause, get worse over time.

Pharmacotherapy is often the central intervention used to improve symptoms or delay the progression of memory impairment. The available agents vary concerning their mechanism of action, adverse and toxic effects, and patient compliance and are supported by varying levels of evidence for therapeutic efficacy. This brief narrative review aims to summarize some of the available information in the field.

Goal: To inform the reader about the pharmacological approaches used in the treatment of memory impairment.

Materials and methods: The inclusion criteria required that the studies explore different pharmacological approaches used in the treatment of memory impairment. Electronic search strategies were developed and undertaken and relevant articles were selected and reviewed.

Results: Over 20 pharmacological agents, showing pharmacotherapeutic relevance, were identified and reviewed in regards to their therapeutic potential, mechanism of action, adverse effects, toxicity, and patient compliance. Some are registered as drugs and others as food supplements. The ones more closely reviewed are Carnitine, Cerebrolysin, Citicoline, Donepezil, Estrogen, Galantamine, Ginko biloba, Haloperidol, Idebenone, Memantine, Metrifonate, Nicergoline, Oxiracetam, Pentoxifylline, Physostigmine, Posatirelin, Propentofylline, Rivastigmine, Selegiline, Tacrine, and Velnacrine.

Conclusion: Memory impairment is a debilitating condition with a high disease burden that can sometimes gradually worsen over a number of years, marring the minds of the ones afflicted at the end leading to profound loss of independence, striking personality changes, and untimely death.
Nevertheless, many pharmacological agents have shown promise for improving memory by modifying physiological processes and interfering with the pathophysiological mechanisms of different diseases. Although currently, there is no definitive prevention or a cure, scientists are on a path to reach these goals, the end of which will be a day to remember!

EXPRESSION OF NGF, BDNF, AND NT3 IN THE SPINAL TRIGEMINAL NUCLEUS IN RATS

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Background: The trigeminal spinal nucleus as part of the trigeminal brainstem nuclear complex consists of three parts – oral, interpolar, and caudal part and it associated with the transmission of discriminative tactile sensations from the orofacial region. The current study focused mainly on the presence of the protein family of neurotrophic factors – nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin3 (NT3) in the spinal trigeminal nucleus in rats. These factors facilitate neuronal differentiation, survival, and plasticity by signaling both through the low-affinity (pan) neurotrophic receptor p75NTR and through high-affinity transmembrane receptors, which are receptor tyrosine kinases (Trk) and are members of the proto-oncogene family.

Materials and methods: The experiments were performed on Wistar rats. Primary antisera/antibodies that were directed against neurotropic factors - NGF, BDNF, and NT3 were used at a dilution of 1: 500. Immunoreactions were visualized with species-specific biotinylated secondary antisera.

Results: As a result of the experiments, we found that the majority of neurons and supporting glia in the spinal trigeminal nucleus of mature rats were NGF-immunopositive. Immunoreactive cells were scattered along the whole length of the nucleus. Immunostaining in the cytoplasm of neurons is pronounced but absent in glial cells. Similarly, BDNF immunostaining is observed in some neurons in the spinal trigeminal nucleus, while NT-3 immunoreactivity was seen in neurons and glial cells.

Conclusion: Our results show that BDNF, NT-3 and NGF immunoreactivities are present in the subnuclei of spinal trigeminal nucleus, which is involved in nociception. It is plausible that these neurotrophic factors are involved in mechanisms of central sensitization in trigeminal nociceptive pathways. Therefore, in addition to neurotrophic factor signaling in the central nervous system, their local paracrine mechanism on spinal trigeminal neurons may provide a novel potential therapeutic target for the treatment of debilitating orofacial pain.

STUDY OF THE NEUROTROPHIC NATURE OF THE CAROTID BODY CELL POPULATION IN SPONTANEOUSLY HYPERTENSIVE RATS

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Introduction: The carotid body (CB) is a small organ located at the carotid bifurcation that senses the chemical composition in the arterial blood. The CB is composed of two cell types, neuron-like glomus cells and glial-like sustentacular cells, which are aggregated in cell clusters and densely innervated by both sensory and autonomic nerve fibers. There is recent physiological evidence that the CB input plays a fundamental role in development of hypertension and that some of the CB adaptive alterations may be explained by the local action of neurotrophic factors.

Aims and Methods: The present study is designed to determine the neurotrophic nature of the CB cell population in the spontaneously hypertensive rat (SHR), which is considered a useful animal model of human essential hypertension. We examined the immunohistochemical localization of some neurotrophic factors and their cognate receptors in rat CB under hypertensive conditions.

Results: Our immunohistochemical experiments revealed the presence of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and their corresponding receptors $p75^{NTR}$, TrkA, TrkB and TrkC in the majority of glomus cells and in a subset of sustentacular cells in the hypertensive CB. In addition, almost all glomus cells expressed glial cell line-derived neurotrophic factor and its corresponding GDNF family receptor alpha1. Moreover, our immunohistochemical analysis revealed that the immunostaining intensity of glomus cells expressing these neurotrophins is considerably increased compared to age-matched normotensive rats.

Conclusions: Our experimental data provides immunohistochemical evidence that the glomus cells under hypertensive conditions may release trophic factors, which contribute to the development of high blood pressure in the rat CB, presumably through a chemoreceptor-related stimulation of its sympathetic activity.

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IN VITRO EFFECTS OF NEWLY SYNTHESIZED 1,3,4-OXADIAZOLE DERIVATIVES, ADMINISTERED ALONE, ON ISOLATED RAT BRAIN SYNAPTOSOMES

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In this study, we investigate the effects of 10 newly synthesized 1,3,4-oxadiazole derivatives, administered alone, on isolated rat brain synaptosomes. The compounds were synthesized by a one-step reaction between acid hydrazides and carboxylic acids, using phosphorus oxychloride ($POCl_3$) as a dehydrating agent. The synaptosomes were obtained by multiple, sub-cellular fractionation by using Percoll gradient. The exam parameters were: synaptosomal viability and level of reduced glutathione (GSH). All compounds revealed weak neurotoxicity. The compounds **3a** and **3d** did not demonstrate any neurotoxic effects. They didn't change the synaptosomal viability and GSH level. The other compounds changed the exam parameters as follows: synaptosomal viability between 15-20 % and GSH level – between 25-30 %, compared to the control (non-treated synaptosomes). The substituents on position 2 of the 1,3,4-oxadiazole ring as 4-chlorophenyl in **3a** and 3-indolyl in **3d** significantly decrease neurotoxicity.

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IN VITRO STUDIES ON ANGIOTENSIN-I CONVERTING ENZYME (ACE) INHIBITORY ACTIVITY OF SHORT SYNTHETIC PEPTIDES

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Hypertension is one of the challenges of modern medicine and is a major risk factor for development of stroke, myocardial infarction, heart failure, arterial aneurysm and peripheral arterial disease. Angiotensin-I converting enzyme (ACE) is an ectoenzyme that plays important role in the regulation of blood pressure and electrolyte balance in the organism by modulating the Renan - Angiotensin system (RAS). It is well known, that there are two isoforms of ACE in human tissue - somatic and testicular ACE. Somatic ACE has two structurally homologous domains (N-and C-), while testicular ACE has a single domain, identical to the C-domain of somatic ACE. There are studies that show differences in the inhibitory and substrate selectivity of the N- and C-domain of human, rat and mouse ACE.

In global aspect there is an increasing interest in isolation of bioactive compounds with antihypertensive action during enzyme hydrolysis of food with different origin – milk protein, egg protein, different cheeses, white and red wine, vegetable proteins and marine sources. It is expected that ACE inhibitors isolated from different natural sources and short synthetic peptides can effectively control blood pressure and while have minimal side effects.

The purpose of the present study was to investigate *in vitro* effects of short bioactive peptides as novel inhibitors of angiotensin-I converting enzyme, which were predicted to possess better activity and lesser side effects.

For the synthesis of each of the target peptides: H-Val-Ala-Trp-OH, H-Val-Ala-Pro-OH, H-Leu-Ala-Pro-OH, H-Leu-Lys-Pro-OH, SPPS were used. The obtained reaction mixtures were purified by HPLC and characterized by UPLC-MS and NMR.

The inhibitory activity of the short peptides was tested *in vitro* on smooth muscle preparations (rat ileum). The effects of the studied compounds were manifested by decrease of the contractions, induced by cumulatively applied Angiotensin I.

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MOLECULAR INSIGHTS INTO THE INTERACTION OF ANGIOTENSIN I-CONVERTING ENZYME (ACE) INHIBITORS AND HEXXH MOTIF

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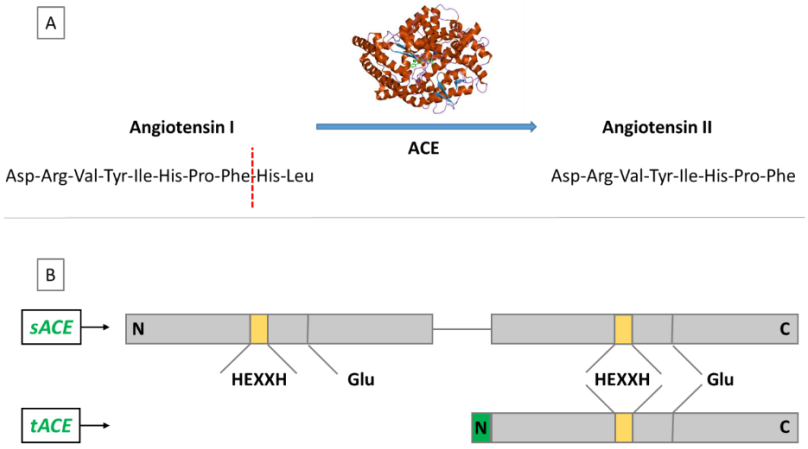
Hypertension is a serious medical condition that significantly increases the risks of heart, brain, kidney and other diseases. Angiotensin I converting enzyme (ACE) is common in human body and is well known for his pivotal role in blood pressure regulation and renal and cardiovascular function. ACE is capable of cleaving wide range of substrates and affects many other physiologic processes in addition to blood pressure control. ACE, classified as **dipeptidyl carboxypeptidase I, is a membrane multifunctional, Zn containing enzyme. It is known that** the so-called somatic form of ACE (sACE) consists of two homologous, independent domains **(C-domain and the N-domain)** each containing a metal-binding motif (HExxH), while the testicular form of the enzyme consists of a single domain (C-domein) **[1]**.



Several synthetic inhibitors as Captopril, Lisinopril, and Enalapril are used in clinical practice for a long time. Numerous studies are also focused on their use as models for studying the enzyme/inhibitor complex for better understanding the inhibition of ACE and to find new more effective therapeutic drugs.

The aim of our study is to model the binding of pharmaceutical drugs Captopril and Lisinopril, and bioactive tripeptide Val-Pro-Pro (VPP) to the HExxH metal-binding motif of ACE. For this purpose, we have applied computational (DFT) methods to assess the ability of Captopril, Lisinopril and VPP to coordinate with Zn^{2+}-HExxH binding region.

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APPLICATION OF MOLECULAR DOCKING FOR PREDICTION THE ACTIVITY OF POTENTIAL μ-OPIOID RECEPTOR LIGANDS

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Opioid receptors are an important class of receptors, and from the day of their discovery until today, efforts have been made to find effective and selective ligands. In recent years, computer-assisted drug design has provided new opportunities for faster screening.

The aim of the present study was to use docking in combination with other assay methods to determine relationships between structure and activity that would allow for the rapid identification of potentially active and selective μ-opioid receptor ligands (MOR).

A docking of 80 known compounds with MOR using GOLD 5.2 was performed. Fitness function, total energies of the formed ligand-receptor complexes were determined and relationships with various physicochemical properties of the compounds, as well as with their biological activity were found.

The obtained results give us reason to place great hopes for the use of molecular docking in the design of selective active ligands of MOR.

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POSTER SESSION “B” BEHAVIORAL AND COGNITIVE NEUROSCIENCES

BENEFICIAL IMPACT OF THE NOVEL MELATONINEGRIC COMPOUND PIROMELATINE ON DEPRESSION AND HYPOTHALAMIC-PITUITARY-ADRENAL AXIS ACTIVITY IN PRENATALLY STRESS MALE OFFSPRING

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There is growing evidence that maternal stress during pregnancy leads to depression development in the offspring across the adult life. With this study we aimed to investigate the effects of piromelatine, a melatonin 1/2 receptor agonist, serotonin 1A/1D receptor agonist, and serotonin 2B receptor antagonist, on prenatally-induced depression and alteration of the feedback mechanism of hypothalamic-pituitary-adrenal axis. Sprague Dawley rats were exposed to stress procedures starting from the 7th day of pregnancy until birth /day 21st/. Piromelatine or vehicle (20mg/kg) was administered for 21 days on 60-day old male offspring. Depression-like behavior was examined in the sucrose consumption (SPT) and the forced swim (FST) tests conducted during the last treatment days. Corticosterone plasma levels for the HPA axishypothalamic-pituitary-adrenal axis activity investigation were determined in 3 consecutive blood samples: before the stressor, at the 10th minute after swimming exposure and 120 min afterward. Offspring rats with a history of prenatal stress demonstrated anhedonia behavior by decreased preference of sucrose consumption, as well as despair-like responses by increased time of immobility in the FST. The increased corticosterone levels after the acute stress remained elevated in the prenatally stressed offspring. Piromelatine treatment alleviated the prenatal stress-induced depressive responses in the offspring showed in both tests together with the restoration of the impaired hypothalamic-pituitary-adrenal axis activity. In conclusion, the novel melatonin analog piromelatine was able to correct the depressive responses through improvement of the impaired feedback regulation of the hypothalamic-pituitary-adrenal axis in offspring male rats.

Acknowledgements: This research was supported by the Bulgarian National Science Fund - grant No. KP 06-H21/10.

EFFECTS OF PIROMELATINE ON MEMORY DEFICITS AND CORTICOSTEROID RECEPTORS ALTERATION INDUCED BY PRENATAL STRESS IN MALE OFFSPRING

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Prenatal stress causes long-lasting hippocampus alternations, which represents a high risk for important adult diseases. With the current investigation we explored the effects of the novel melatoninergic compound piromelatine, known also to possess serotonin (5-HT) 1A/1D receptor agonistic and 5-HT2B receptor antagonistic activity, on memory and corticosteroid receptors alterations associated with prenatal stress. Different types of stressors were applied on pregnant female Sprague Dawley rats starting from the 7th gestational day until birth /day 21st/. Adult male offspring were injected with piromelatine or vehicle (20mg/kg) daily for 21 consecutive days. Spatial memory was examined in the radial arm maze test (RAM), performed during the last treatment days. Glucocorticoid receptors (GR) and mineralocorticoid receptors MR) were measured in both hippocampi by ELISA kit (DLDevelop, China) in ng/mg protein according to the instructions of the manufacturer. Rats exposed to prenatal stress demonstrated spatial memory deficit compared to their controls. The prenatal stress resulted in a significant increase of the expression of both corticoid receptors. Piromelatine treatment improved the altered memory function in the prenatally stressed offspring, showed by decreased working memory errors. This drug reversed to control level the prenatally stressed-induced alterations of MR and GR receptors in the adult offspring. Our findings suggest that the novel drug piromelatine can beneficially impact the hippocampal plasticity and improve memory performance in male offspring with a history of prenatal stres.

Acknowledgements: This research was supported by the Bulgarian National Science Fund - grant No. KP 06-H21/10.

EVALUATION OF NEUROBIOLOGICAL AND ANTIOXIDANT EFFECTS OF NOVEL MELATONIN ANALOGS IN MICE

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We recently synthesized a series of indole derivatives that showed anticonvulsant activity with low neurotoxicity and hepatotoxicity in rodents. Based on the pharmacophore model of melatonin (MT1) receptor in the present study, the three most potent C3-modified derivatives with hydrazide structure **3c**, **3e**, and **3f**, with 2-chlorophenyl, 2-furyl, and 2-thienyl fragments, respectively, were selected, and their neurobiological activity was explored in mice. In Experiment #1, the dose-dependent anxiolytic effect of a single i.p. administration of the novel compounds at doses of 10, 30, and 60 mg/kg were studied in the open field (OF) test. In Experiment#2, the analgesic effect of **3c**, **3e**, and **3f** (30-100 mg/kg) was tested in the hot plate test and formalin test. Experiment#3 was designed to assess the antidepressant-like activity of **3c**, **3e**, and **3f** (10-60 mg/kg). The forced swimming test (FST) and tail suspension test (TST)-induced effect on markers of oxidative stress in the frontal cortex (FC), and the hippocampus was evaluated. Melatonin was used in the same doses as melatonin analogs in all three experiments as a positive control. Desipramine (10 mg/kg) was also applied as a control in the FST. The three melatonin analogs bearing hydrazide/hydrazone substitution at 3C of the indol scaffold demonstrated improved antidepressant-like activity compared to the melatonin. The antioxidant activity of the melatonin analogs in vivo and analgesic potential is comparable to that of melatonin. The 3C substitution with hydrazide/hydrazone moiety substantially contributes to the antidepressant and antioxidant activity of the melatonin analogs. The tested substances are devoided of anxiolytic effects.

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ANTIOXIDANT ACTIVITY OF MAGNETIC NANOPARTICLES AND MAGNETIC FIELD IN RODENTS

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Electro-magnetic treatment is a non-invasive physical process based on magnetic field interaction with iron oxide magnetic nanoparticles (MNPs), which can be used in the field of diagnosis and treatment of many diseases. Over-production of reactive oxygen species (ROS) weakens enzymatic and nonenzymatic antioxidant defense systems of the living body that may cause many numerous disorders, such as neurodegenerative, cardiovascular and hepatic. The goal of the current work was to assess the impact of a pulsed magnetic field (PMF) in the presence of MNPs (Fluid MAG-D) on redox homeostasis in mice. The animals were simultaneously treated intracerebroventricularly with MNPs at doses of 100 and 200 μg/kg and exposed to PMF for 30 min. The mice were decapitated and the hippocampus was isolated at the 3^{th}h, 24^{nd} h and 48^{th} h, respectively, for analysis of the superoxide dismutase (SOD) activity and the lipid peroxidation end product malondialdehyde (MDA). The higher antioxidant activity of SOD was detected after 3h of treatment for samles containing 200 μg/kg MNPs and for those of combined treatment with MNPs and PMF. Then, SOD activity was decreased below the levels of the control groups after 24^{th} h and 48^{th} h of treatment for all groups. No significant difference was found for the MDA levels in rodents treated with MNPs. However, a slight increase of the levels of MDA was detected for groups of enimals treated with PMF or with combination of PMF and MNPs, which was more expressed in the earliest hours after treatemt. Together, the results indicate that the simultaneous application of PMF and MNPs increase antioxidant potential against the harmful active radical species in the tested animals. Thus, the above treatment could be used safely for application in different therapies or diagnostic purposes.

Acknowledgments: This work was supported by National Research Program "Young scientists and postdoctoral students (DCM#577/17.08.2018)" - Bulgarian Ministry of Education and Science.

EEG CORRELATES OF AGE-RELATED GENDER DIFFERENCES IN AUDITORY SELECTIVE ATTENTION

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Background: There is evidence that a variety of brain functions depend on gender. However, it is not well understood if and how these neurofunctional gender differences change in the course of development during childhood and adolescence (Lenroot and Giedd, 2010). The aim of the current research was to compare the gender-dependent developmental trajectories of selective attention processes in children and adolescents using event-related potentials (ERP) as objective neurophysiological indices of information processing in the brain. ***Methods***: Subjects were 110 healthy, right-handed 9-16 years-old boys and girls (55 boys), divided in 4 age groups (9-10, 11-12, 13-14, 15-16 year-olds). They performed an auditory selective attention task, where maintaining of lateralized inner attention, and selective motor reaction to target stimulus characteristics were required. ERPs were recorded and analyzed at 8 electrodes (F3, Fz, F4, C3, Cz, C4, P3, P4). ***Results***: Behavioral results: Reaction times (RT) did not depend significantly on gender. Early ERP components: N1 and P2 latencies were overall shorter in girls than boys. Late ERP components: N2 and P3 latencies were also shorter in girls than boys. Parietal N2 and P3 latency decreased in the course of development, in girls starting at 9 years of age and in boys – two years later. N2P3 amplitude was larger in girls than boys, and this gender difference did not depend on age. ***Conclusions***: The results demonstrate that both early (perceptual) and late (cognitive) stages of selective attention depend on gender, being faster and more intensive in girls than boys. The age-related acceleration of selective attention mechanisms is delayed by two years in boys compared to girls.

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PROCESSING STRATEGIES IN DUAL-TASKING: AGING-RELATED SIMILARITIES AND DIFFERENCES

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Typically, everyday tasks are complex and consist of a sequence of multiple sub-tasks. There is evidence that the temporal organization of sub-tasks in a goal-directed order is a key element of successful performance. The task-order set (TOS) can be regarded as a hyper-construct, the maintenance of which improves performance. The objective of this research was to clarify how the functioning of TOS depends on increasing age in humans. The psychological refractory period (PRP) task was used, in which two target stimuli (T1 and T2) were presented in rapid succession and required different responses R1 and R2. T1-R1 and T2-R2 formed two different non-overlapping sub-tasks (dual task). In this task, when the interval (SOA) between T1 and T2 is manipulated, the R1 is not affected by SOA, whereas the R2 decreases as SOA increases. This PRP effect is assumed to reflect the formation and functioning of TOS neural representations. Here, the PRP effect was analyzed in young (n=35) and older adults (n=130) who performed blocks with fixed and mixed task order, with SOA being 0 or 750 ms. The PRP effect was strongly expressed in young adults and persisted in fixed-TOS, cued mixed-TOS, and non-cued mixed-TOS conditions. The PRP effect was evident in older adults, validating the functional efficiency of TOS. However, in each condition, the PRP effect was significantly smaller in older relative to young adults, indicating a reduced role of the temporal order for the control of performance in aged subjects.

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EFFECTS OF AGING ON MOTOR THETA NETWORKS

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Alterations in medial frontal theta (3.5-7 Hz) oscillations may account for aging-related differences in error processing and movement monitoring. However, it has been also suggested that a distributed oscillatory theta system in the brain plays a major role in coordinating motor actions. Here, neurodynamics of motor theta oscillations elicited by correct responses in choice-reaction tasks was analyzed to test if theta activity at motor cortical regions is also changed in aged individuals, similarly to error-related theta oscillations. Response-related potentials (RRPs) generated by left- and right-hand responses of young and older adults were analyzed in the time-frequency domain. The phase-locking factor and total power of theta RRPs were computed at motor cortical regions contra- and ipsilateral to the movement and at the midline. Major results demonstrated that in both young and older adults, a pronounced response-locked theta activity was generated at premotor, motor and sensorimotor cortical regions contra-lateral to the responding hand. Aging was associated with a decreased lateral asymmetry in the phase synchronization of only the left-hand responses. Also, there was a strong aging-related suppression of theta power at the medial fronto-central region, but phase synchronization did not depend on aging, in contrast to error-related findings. These results show that aging is associated with a dysfunction of the oscillatory theta system for motor action regulation and monitoring due to a strong suppression of a medial frontal integrating mechanism. Also, aging impairs the balance in the functional control of responses with the right and the left hand.

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TOPOLOGICAL CHARACTERISTICS OF NEURAL MANIFOLDS

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Background: There are several types of neurons which function as feature detectors and play an important role in population coding and decoding (Kriegeskorte 2019). Based on theoretical arguments it is also expected that they are distributed on smooth manifolds and that the relationships between the features should be the same as those between the neural states representing them (Curto 2017). In order to model such representational surfaces with neural networks we extend the neural field models of Wilson and Cowan 1972 to respond to features coming from a well-behaved manifold. We are also able to validate whether our models are truly able to code the features on a given manifold with a new technique from *topological data analysis* (TDA) called *persistent homology* (Carlsson 2009) which counts the number and dimensions of the different holes in the manifold traced out by the position of each neuron in representation space. ***Methods***: We defined the model by the equations for the adaptive neural field model with Mexican-hat connectivity in (Coombes et. al. 2014). The difference being that we worked with an activity based version of the model and more importantly the distance function on which the weights are based was given by the shortest curves (geodesics) on the feature manifold. To solve these equations we ran these models with the underlying feature spaces being different manifolds for which we calculated the geodesics and used a fourth order Runge-Kutta method to solve the equations in Python. To analyze whether they are able to reproduce the topology of a feature space, we used the package Ripser (Tralie et. al. 2018) to compute the *persistent homology* of the resulting manifold. One difficulty we stumbled upon was that the model required dense and equidistant sampling of the feature manifold. ***Results***: We found that the models were capable of reproducing the topology of the circle and the sphere. We also found that it correctly implemented continuous transformations between separate network layers, for example a transformation from a sphere to a circle. This result points to the possibility that neural networks implement successive transformations of their neural manifolds through different layers, thereby also transforming the representations that said layers contain.
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EVALUATION OF VISUAL-MOTOR INTEGRATION IN THE PERFORMANCE OF A DECECISION-MAKING TASK AFTER THE APPLICATION OF SEMANTIC PRIMING FOR WIDE ATTENTION FOCUS

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The aim of the present study was to evaluate the influence of semantic priming associated with unconscious induction of cognitive attention (Bargh et al., 1996) on visual-motor task related to attention participation. The applied priming is based on a modified test consisting of sentences with mixed words, one of which expresses a wide focus of attention. The participants (who are not familiar with the specific purpose of the study) should arrange them in a meaningful sentence (Bock et all, 2016). The effect that priming has on the response time (RT) in the visual-motor task of the hand (VMHT) in decision-making in traffic test scenarios for non-professional drivers was evaluated. Twenty young participants (YP) and twenty elderly participants (OP), divided into subgroups of 10 people, were studied under two conditions of priming application:

1) Immediately before the cognitive visual-motor task (YP and OP);
2) After adaptation of reactive visual saccades, before which the semantic priming (YS and OS) was applied. Another twenty participants (10 young and 10 elderly) were the non-primed control groups (YC and OC). The traffic test scenarios are displayed either in full screen or in the central part (25% of the screen).

The results show:
1) the RT of the two groups, YP and OP, are higher than the RT of the respective control groups, while the RT of the YS and OS groups are shorter than those of the respective control groups;
2) RT of both groups of adult subjects (OP and OS) is significantly higher than RT of the groups of young subjects (YP and YS); 3) RTs of all groups are larger in large pictures than in small ones.
We assume that the negative effect of semantic priming on the visual-motor task related to decision-making is conditioned by the subtraction of cognitive resources from the directly applied priming, which also includes decision-making. Therefore, priming and the subsequent visual-motor task are related and the effect of the former on the latter depends on the type of cognitive resources they need.

ASSESSMENT OF COLOUR DISCRIMINATION IN HYPOTHYROIDISM AFTER DRUG TREATMENT USING FM 100 TEST

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In our previous study colour discrimination was assessed using the Farnsworth–Munsell 100 hue test (FM 100) in patients with hypothyroidism (decreased thyroid function). Untreated hypothyroidism was found to lead to colour vision deficits in the blue-yellow area in hypothyroid group compared to the control group without thyroid dysfunction. The hypothyroid group had significantly greater partial error scores (√PES) along the blue-yellow (B-Y) axis compared to the red-green (R-G) axis, while there was no statistically significant difference in the total error score (√TES) between both groups [Racheva et al. (2020), JOSA 37 (4), A18 – A25].

In the present study, the assessment of color discrimination with the FM100 test was repeated with part of the hypothyroid subjects who had been treated with Levothyroxine for at least one year and had reached biochemical euthyroidism. Contrary to the results from the previous study, the obtained data show no statistically significant difference in √PES for B-Y (4.61) and R-G (4.51) axis ($p=0.84$). Also, the results are close to those of the control group (√PES for B-Y=4.88, $p=0.75$ and R-G=4.50, $p=0.96$). Therefore, the drug treatment with Levothyroxine most likely alleviates color vision deficits in patients with hypothyroidism.

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AGE-RELATED CHANGES IN EYE MOVEMENTS' CHARACTERISTICS IN DECISION-MAKING AND CLASSIFICATION TASKS

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In classification tasks, the stimuli are divided into different groups based on a selection of their features. Different cognitive processes are involved in task performance including the processing of the sensory information, attention, decision making, memory and learning of the stimulus-response associations from the repeated presentation of the stimuli and the received feedback. In a set of experiments, we recorded the eye movements of two age groups: 15 young (18 - 38 yrs) and 14 elderly (63 – 75 yrs) participants during the classification of visual stimuli in tasks of varying difficulty. We aimed to obtain additional information about the age effects on decision-making and classification processes from the eye movements' parameters. Three experiments were performed. The stimuli differed by the combination of four characteristics - type and direction of movement, color, and shape of the elements. In Experiment 1 the classification is determined by the color of the elements, in Experiment 2 - by the combination of direction and type of motion, and in Experiment 3 - by the combination of color, direction, and type of motion.

The results show that the elderly group made more saccades in all experimental conditions with the largest difference between the two age groups for Experiment 1. For both age groups, the number of saccades depends on the task difficulty, being largest for Experiment 3. The results suggest a longer response time and latency of the first saccade for the elderly group. While for the young subjects the response time differed from the latency of the first saccade and depended on the difficulty of the experiment, for the elderly group there was no significant difference in response time in different experimental conditions. The results suggest age differences in the decision-making processes in classification tasks that could be better evaluated and understood from the information of eye movements.

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THE EFFECT OF EXTERNAL NOISE ON THE MOTION DIRECTION SENSITIVITY IN CHILDREN AND ADOLESCENTS WITH DEVELOPMENTAL DYSLEXIA

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The present study aims to study the effect of external visual noise on motion direction sensitivity of children and adolescents with Developmental Dyslexia (DD). To achieve this aim, we used the method of equivalent noise to compare the ability of participants with DD and typical development (TD) to integrate global motion information. Two groups of subjects were tested – 17 children with DD (mean age - 9.76) and 17 TD children (mean age - 9.82). Our stimuli were patterns of 30 band-pass of elements moving at a speed of 4˚/s. The individual stimulus elements moved in different directions selected from a normal distribution with a standard deviation of 2˚, 5˚, 10˚, 15˚, 25˚, 35˚. A Double Staircase procedure, combined with a two-alternative forced choice method was used to measure a discrimination threshold. The subject's task was to determine whether the mean motion direction was to the left or to the right of the vertical.

Results obtained show smaller individual differences in the external noise effect in the group with DD than in the control group. There are statistically significant differences in a sensitivity to global motion direction between DD and TD participants. The group with DD shows lower sensitivity to global motion direction, which is due to reduced efficiency in visual motion information integration rather than to a greater inaccuracy in local direction estimation.

In conclusion, the experimental findings show similar internal noise in the DD and TD groups, but imply impaired ability to integrate visual motion information in participants with dyslexia.

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EFFECT OF AGE IN SINGLE- AND MULTI-CUE CLASSIFICATION TASKS

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Classification of objects or events in groups plays a key role in survival as well as in everyday life. Categorization learning is explored in a huge variety of ways that differs by the structure of the categories, the rule of association between stimulus and response, and provided feedback. On the other hand, it is known that cognitive abilities change with age. Our aim is to investigate the effects of the age and task complexity on unstructured category learning with single- and multi-cue classification rules. The stimuli consisted of randomly distributed colored elements (blue, red, yellow and green spheres or cubes) forming 2D or 3D colored dynamic patterns that moved either to the left, to the right, forward or backward. Thus the stimuli differed by 4 characteristics: color, motion direction, the dimensionality of the pattern, and shape of the elements. We conducted 3 category learning experiments which differed by the classification rule used to separate the stimuli in two categories. The stimuli were divided by: the pattern color (Experiment 1); the combination of motion direction and pattern dimensionality (Experiment 2); the combination of color, motion direction, and dimensionality of the pattern (Experiment 3). In all experiments the shape of the elements was irrelevant to the classification. 16 young (Md = 22 years) and 17 old (Md=67 years) observers participated in the experiments. They learned to classify the dynamic pattern stimuli into two categories by trial and error with incomplete deterministic feedback provided by a sound signal after each trial. All observers were naive about the classification rules. The results show that regardless of large inter-individual differences in performance, the highest accuracy and shortest response time are reached in single-cue categorization task by pattern color. As the number of cues increases the learning performance deteriorates and it is worst in triple-cue classification by combination of color, motion, and dimensionality of the pattern. In all conditions the young observers achieve a higher proportion of correct responses and shorter response time than the old. As the complexity of the task increases, the learning performances of the young and old group are getting closer although some of the young observers performed the task by reducing its complexity from a triple-cue task to a rule-plus-one-exception task.

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A DEGRADATION OF WORDS AND PSEUDOWORDS AFFECTS DIFFERENTLY THE READING SPEED AND ACCURACY IN ASD AND DD

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Understanding the factors that determine reading failure is important for successful identification of deficits that may vary in different developmental disorders. A condition of Developmental Dyslexia (DD) is most often associated with reading difficulties. Although the core deficit of Autism Spectrum Disorder (ASD) is in social domains, many children with ASD have diminished language skills. The aim of our study was to evaluate whether the impaired reading performance in both disorders in comparison to typical development (TD) may be due to their compromised ability to filter external perceptual noise and/or to increased neural variability. To this aim the reading speed and proportion of errors were compared in children and adolescents with DD, ASD or TD. Test samples were degraded using positional noise of letter position below or above the horizontal line. The results obtained showed that the external visual noise affected reading of all groups of participants in a different way, with the strongest effect on ASD group. Possible sources of external noise effect could be connected to the compromised noise filtering, increased neural variability, and crowding. A comparison between reading words and pseudowords at different noise levels suggests possibility for a transition between using lexical and sublexical pathways at high noise level. The relationship between the proportion of correctly read words and pseudowords and the reading time implies a strong link between the reading rate and accuracy, which is different for the groups with different development.

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