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NEURONUS 2022
NEUROSCIENCE FORUM
SUPPORTED BY IBRO

15–17 OCTOBER 2022, KRAKOW, POLAND

NENCKI INSTITUTE OF EXPERIMENTAL BIOLOGY PAS WARSAW, POLAND

ACTA NEUROBIOLOGIAE EXPERIMENTALIS

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NEURONUS 2022
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PROGRAMME

14TH OCTOBER, 2022
INSTITUTE OF PSYCHOLOGY OF JAGIELLONIAN UNIVERSITY

Workshop I – *Room 2.15*
DeepLabCut by Jessy Lauer
(Swiss Federal Institute of Technology, Lausanne, Switzerland & Harvard University, USA)

Workshop II – *Room 2.12*
Multimodal recordings: an insight into combining EEG with eye tracking and other research methods
sponsored by Brain Products Academy and Elmiko Biosignals

15TH OCTOBER, 2022
AUDITORIUM MAXIMUM, JAGIELLONIAN UNIVERSITY

9:00–10:10 **Opening Ceremony – *Large hall A***
Vice Rector for University Development, Jagiellonian University
prof. Jarosław Górniak
Vice-Dean for Science and International Relations, Faculty of Biology, Jagiellonian University
prof. Magdalena Chadzińska

Keynote lecture – *Large hall A*
Childhood physical activity effects on brain health and cognition
Speaker: Charles Hillman (Department of Psychology, Department of Physical Therapy, Movement, and Rehabilitation Sciences, Northeastern University, USA)

10:10–10:45 **Flashtalks – *Large hall A***

10:45–11:15 **Coffee Break**

11:15–13:15 **Special Biological Session I – *Large hall A***
Astrocytes
Speakers: Alexei Verkhratsky, Mykhailo Batiuk, Dmitri Rusakov, Olena Bukalo

Cognitive Session I – *Large hall B*
How does exercise benefit cognition and emotion?
Speakers: Irene Estaban-Cornejo, Tomasz Ligęza, Dominika Pindus, Angelika Maurer

13:15–13:45 **Lunch**

13:45–15:00 **Poster Session I – *Exhibition room***

15:00–16:00 **Keynote lecture – *Large hall A***
From a demand-based to a supply-limited view of brain energetics
Speaker: Suzana Herculano-Houzel (Department of Psychology and Biological Sciences, Vanderbilt University, USA)

16:00–17:30 **Biological Session II – *Large hall A***
Basic Neuroscience
Speakers: Aleksandra Pękowska, Katarzyna Ciuba, Michael Gabriel, Joanna Danielewicz

Cognitive Session II – *Large hall B*
Emotional processing in modern neuroscience – from human-rat dyads to VR devices
Speakers: Magdalena Pietruch, Malwina Ankiewicz, Jan Argasiński, Anna Kaźmierowska, Ingrida Zelionkaite

Medical Session I – *Medium hall A*
Biomarkers of Neurodegeneration
Speakers: Kaj Blennow, Fernando Gonzalez-Ortiz, Przemysław Kac, Patrycja Dzianok

17:30–18:00 **Coffee Break**

18:00–19:00 **Keynote lecture – *Large hall A***
The cinematic brain: Mapping the human emotion circuits with motion pictures
Speaker: Lauri Nummenmaa (Human Emotion Systems Laboratory at Turku PET Centre, Finland)

19:00– **Welcome Reception**

16TH OCTOBER, 2022
AUDITORIUM MAXIMUM, JAGIELLONIAN UNIVERSITY

7:00–8:00 **Run for your brain!**
Parking lot in front of the Institute of Psychology of the Jagiellonian University, 6 Ingardena Street
Neu-run-us

9:00–10:00 **Keynote lecture – *Large hall A***
Routes to enhance stress resilience: Manipulation of genes or environment?
Speaker: Mathias Schmidt (Max Planck Institute of Psychiatry, Munich, Germany)

10:00–11:30 **Biological Session III – *Large hall A***
Neural substrates of affective behavior
Speakers: Marcelina Olga Węzik, Natalia Roszkowska, Olga Gulka, Karolina Protokowicz, Patryk Sambak

Cognitive Session III – *Large hall B*
Approaches to increase replicability in neuroscience – lessons learned from consortia, many analysts and cooperative data collection
Speakers: Sven Mueller, Katharina Paul, Elena Cesnaite, Vanja Kovic

Biological Session IV – *Medium hall A*
Markers of Aging
Speakers: Urszula Wojda, Natalia Pudełko-Malik, Anna Mietelska-Porowska, Gregory Petrazzo

11:30–12:00 **Coffee Break**

12:00–13:30 **Biological Session V – *Large hall A***
Advanced neurotechnologies for brain activity monitoring and modulation
Speakers: Richárd Fiáth, Csaba Horváth, Zsófia Lantos, Kirti Sharma

Cognitive Session IV – *Large hall B*
Plastic brain and language – adaptive changes of neural networks
Speakers: Aleksandra Herman, Marta Wójcik, Agata Wolna, Jonas Walther, Anna Stróż

Medical Session II – *Medium hall A*
Translational Neuropsychiatry
Speakers: Ali Jawaid, Weronika Tomaszewska, Kinga Farkas, Katarzyna Hryniewiecka, Suelen Baggio, Sabina Podlewska

13:30–14:00 **Lunch**

14:00–15:15 **Poster Session II – *Exhibition hall***

15:15–17:00 **Biological Session VI – *Large hall A***
Systems Neuroscience of Sensory Processing
Speakers: Flavio Donato, Bartosz Zglinicki, Magdalena Sabat, Maciej Kania, Marek Brodzki

Cognitive Session V – *Large hall B*
Neuroimaging of the reading brain
Speakers: Milene Bonte, Katarzyna Chyl, Agnieszka Dębska, Agnieszka Glica, Katarzyna Wasilewska

Computational Session I – *Medium hall A*
New methods in MRI
Speakers: Rita Nunes, Michał Rafał Zaręba, Dominika Ciupek, Marcin Sińczuk, Alaa Alghanimy

17:00–17:30 **Coffee Break**

17:30–18:30 **Keynote lecture – *Large hall A***
Fish feelings: Motivational internal states in larval zebrafish
Speaker: Florian Engert (Department of Molecular and Cellular Biology, Center for Brain Science, Harvard University, USA)

20:30– **Neuronus Party**

17TH OCTOBER, 2022
AUDITORIUM MAXIMUM, JAGIELLONIAN UNIVERSITY

9:00–10:00 **Keynote lecture – *Large hall A***
Diversity of oxytocin circuits modulating distinct socio-emotional behaviors
Speaker: Valery Grinevich (Central Institute of Mental Health, University of Heidelberg, Germany)

10:00–11:30 **Biological Session VII – *Large hall A***
Hypothalamic control of behavior
Speakers: Frank Meye, Karolina Hajdukiewicz, Emilia Gawron, Alan Kania

Cognitive Session VI – *Large hall B*
Search for neural biomarkers of aware consciousness
Speakers: Ilona Kotlewska, Łucja Doradzińska, Karolina Golec, Julia Papiernik, Klaudia Krystecka

Medical Session III – *Medium hall A*
Novel targets in retinal ganglion cell neuroprotection
Speakers: Marialaura Amadio, Piotr Rodak, Joanna Machowicz, Anna Pacwa

11:30–12:00 **Coffee Break**

12:00–13:30 **Biological Session VIII – *Large hall A***
Mitochondrial dysfunctions in neurological disorders
Speakers: Alessandro Prigione, Sinéad A. O'Sullivan, Aleksandra Stawikowska, Carla Ramon

Cognitive Session VII – *Large hall B*
Pupillometry: Getting information in the glimpse of an eye
Speakers: Alexandre Zénon, Beaupoil Laurent, Bartłomiej Król-Józaga, Monika Riegel, Jakub Cacek

13:30–14:00 **Lunch**

14:00–15:15 **Poster Session III – *Exhibition hall***

15:15–16:30 **Biological Session IX – *Large hall A***
Blood-brain barrier
Speakers: Aleksandra Rutkowska, Fionä Caratis, Jakub Jurczyk, Ewelina Czuba

Cognitive Session VIII – *Large hall B*
Specificity of language network in the contingentally blind brain
Speakers: Maksymilian Korczyk, Marta Urbaniak, Dominika Radziun, Łukasz Bola, Jacek Matuszewski

Computational Session II – *Medium hall A*
Novel methods in EEG
Speakers: Joanna Duda-Goławska, Piotr Biegański, Anna Grabowska, Nikodem Hryniewicz, Sandra Frycz

16:30–17:00 **Coffee Break**

17:00–18:00 **Keynote lecture – *Large hall A***
Built to learn: Insights into nature and nurture from studies with people born blind and cultural expertise
Speaker: Marina Bedny (Department of Psychological and Brain Sciences, Johns Hopkins University, USA)

18:00–18:15 **Awards & Closing Ceremony – *Large hall A***

KEYNOTE SPEAKERS

THE CINEMATIC BRAIN: MAPPING THE HUMAN EMOTION CIRCUITS WITH MOTION PICTURES

Lauri Nummenmaa

Human Emotion Systems Laboratory at Turku PET Centre, Finland

Emotions promote our well-being in survival-salient situations. They are triggered by biologically relevant signals such as threats and physical harm or rewards including food consumption or social interaction. Yet, also abstract and "simulated" pleasures and threats such as love stories, misfortunes, and tragedies shown in films can trigger powerful emotions in the viewers. In my talk I present an overview on brain mechanisms supporting human emotions and show how we can use cinema for simulating real life for studying the emotional brain. I present data from our laboratory showing how viewing emotions in films makes individuals to "tune in" with each other, and how specific neurotransmitter systems in the brain govern out vicarious experience of the emotions we see in movies. Finally, I discuss the origins of our captivation for strong, sometimes also distressing and unpleasant, emotional movies. I propose that we are drawn to affective cinema because it provides a safe simulation environment for preparing to meet actual emotional challenges in real life.

FISH FEELINGS: MOTIVATIONAL INTERNAL STATES IN LARVAL ZEBRAFISH

Florian Engert

Department of Molecular and Cellular Biology, Center for Brain Science, Harvard University, USA

I will discuss how motivational states in larval zebrafish can regulate specific switching between behavioral priorities. In the first part I will explain how the oxytocin system regulates and relays processing of aversive and noxious stimuli, and how this can be extended to states of social isolation. In the second part I will share our results on the role of hypothalamic serotonergic neurons in the regulation of hunger and its influence on switching between exploit *vs* explore strategies.

BUILT TO LEARN: INSIGHTS INTO NATURE AND NURTURE FROM STUDIES WITH PEOPLE BORN BLIND AND CULTURAL EXPERTISE

Marina Bedny

Department of Psychological and Brain Sciences, Johns Hopkins University, USA

Humans are unique among animals both in their advanced shared cognitive capabilities and in their remarkable ability to adapt to diverse environments. Studies with people who are born blind provide insights into the biological and cognitive origins of the human flexibility/specificity sweet-spot. Contrary to the suppositions of early empiricist philosophers, blind and sighted people share rich 'visual' knowledge, including knowledge of color. Such evidence is inconsistent with accounts of development that emphasize bottom up sensory learning. Instead, blindness illustrates the power of uniquely human social, linguistic and inferential learning. On the other hand, evidence from blindness reveals the remarkable flexibility of the human brain. 'Visual' occipital cortices serve drastically different cognitive functions across sighted and congenitally blind people: visual perception in the sighted, higher-order cognition in people born blind. Visual cortex plasticity suggests 'wetware pluripotency' at birth. Blindness is just one example of the human brain adapting to change, supporting cultural inventions such as reading, math and computer programming. There is no such thing as a 'normal' brain. Instead, we are born with a protobrain that is built to learn and adapt to our particular environment.

FROM A DEMAND-BASED TO A SUPPLY-LIMITED VIEW OF BRAIN ENERGETICS

Suzana Herculano-Houzel

Department of Psychology and Biological Sciences, Vanderbilt University, USA

The brain is an expensive organ, which is usually attributed to the energetic "needs" of the excitable neuronal cells that compose it. This talk presents evidence that brain function should be considered differently: as an economy that is limited by the rate at which energy is supplied by the microvasculature, with implications for brain physiology, development, and evolution.

ROUTES TO ENHANCE STRESS RESILIENCE: MANIPULATION OF GENES OR ENVIRONMENT?

Mathias V. Schmidt

Max Planck Institute of Psychiatry, Munich, Germany

The increasing rate of stress-related disorders, with mood disorders as major depression leading the way, and the social and well as economic consequences of these illnesses represent a growing threat to our society. A dysregulation of the body's main stress system, the hypothalamic-pituitary-adrenal axis, is a major hallmark of depression, but so far no specific treatments tackling this mechanism are available. It seems clear that genetic predispositions interact with environmental demands such as chronic stress and modulate the long-term health outcome. In addition, there is abundant evidence that environmental

circumstances early in life are capable of shaping the adult phenotype. Here I will discuss two aspects that can shape stress resilience: genetic predisposition and experiences during early life. Firstly, I will focus on the co-chaperone FK506-binding protein 51 (FKBP51) as a very promising target molecule for new drug therapies, as it is highly linked to stress-related human disorders, directly regulates stress hormone activity and metabolic disturbances. Secondly, I will address the influence of the early life environment on later stress resilience or vulnerability dependent on genetic background. Taken together, our results now pave the way for tailored and specific treatment strategies that could be beneficial for improving stress resilience in health and disease.

DIVERSITY OF OXYTOCIN CIRCUITS MODULATING DISTINCT SOCIO-EMOTIONAL BEHAVIORS

Valery Grinevich

Central Institute of Mental Health, University of Heidelberg, Germany

Neuropeptides represent a new class of non-canonical neurotransmitters, which dramatically challenge a plethora behavioral and homeostatic functions. Among a hundred of identified neuropeptides, oxytocin remains the best studied molecule due to a great attention of the general public, basic neuroscience researchers, psychologists and psychiatrists based on its profound pro-social and anxiolytic effects. During the last decade, a substantial progress has been achieved in understanding the complex neurobiology of the brain oxytocin system. However, the picture of oxytocin actions remains far from being complete, and the central question remains: "How does a single neuropeptide exert such pleiotropic actions?". In this lecture, I will tackle this question, demonstrating the anatomical divergence of oxytocin neurons and their numerous central projections. In conjunction, I will describe unique composition of distinct oxytocin-sensitive neurons in different brain regions, modulating distinct forms of behaviors. At the end, I will emphasize advantages and great potencies of oxytocin – in comparison to other neuropeptides – for its use for treatment of human mental disorders.

CHILDHOOD PHYSICAL ACTIVITY EFFECTS ON BRAIN HEALTH AND COGNITION

Charles Hillman

Department of Psychology, Department of Physical Therapy, Movement, And Rehabilitation Sciences, Northeastern University, USA

There is a growing public health burden of unhealthy behaviors (e.g., physical inactivity, excessive energy intake) among children of industrialized nations. Children have become increasingly inactive, leading to concomitant increases in the prevalence of being overweight and unfit. Poor physical activity behaviors during childhood often track throughout life and have implications for the prevalence of several chronic diseases during adulthood. Particularly troubling is the absence of public health concern for the effect of physical inactivity on cognitive and brain health. It is curious that this has not emerged as a larger societal issue, given its clear relation to childhood obesity and other health disorders that have captured public attention. My research program has investigated the relation of health behaviors (e.g., physical activity, exercise) and their related physiological correlates (e.g., aerobic fitness, adiposity) to cognitive and brain health in preadolescent children. My techniques of investigation involve a combination of neuroimaging, behavioral assessments, and scholastic outcomes in an effort to translate basic laboratory findings into everyday life. Central to this translational approach is the identification of etiological substrates of brain regions and networks that are susceptible to health behaviors. As such, the overarching goal of my research is to determine factors that improve cognition, maximize brain health, and promote the effective functioning of individuals as they progress through the lifespan. Findings from my studies have indicated that greater aerobic fitness and healthy body mass are positively related to brain structure and function, cognition, and scholastic achievement. Such discoveries are timely and important for public health concerns related to chronic disease prevention as a function of childhood inactivity and obesity. These findings link pervasive societal concerns with brain health and cognition, and have implications for the educational environment and the context of learning.

BIOLOGICAL SESSION 1

Astrocytes

Symposium organizer: Michał Ślęzak
(*Łukasiewicz Research Network, PORT Polish Center for Technology Development, Poland*)

PHYSIOLOGY OF ASTROGLIA

Alexej Verkhratsky

Faculty of Life Sciences, The University of Manchester, UK

The integration and information processing in the brain occurs though close interactions of two cellular circuits represented by neuronal networks embedded

into internally connected astroglial syncytia. Our understanding of glial function changed dramatically over last two decades. This change concerns the whole concept of how the brain is organized, and how the development, life and death of neural circuits are controlled. There is compelling evidence demonstrating that these are the astrocytes that are creating the compartmentalisation in the CNS, and these are the astrocytes that are able to integrate neurones, synapses, and brain capillaries into individual and relatively independent units. Astroglial syncytia allow intercellular communication routes, which permit translocation of ions, metabolic factors and second messengers. The resulting potential for parallel processing and integration is significant and might easily be larger, but also fuzzier, than the binary coded electrical communication within the neuronal networks. The neuronal-glial circuitry endowed with distinct signalling cascades, form a "diffuse nervous net" suggested by Golgi, where millions of synapses belonging to very different neurones are integrated first into neuronal-glial-vascular units and then into more complex structures connected through glial syncytia. These many levels of integration, both morphological and functional, presented by neuronal-glial circuitry ensure the spatial and temporal multiplication of brain cognitive power.

ADAPTABLE ASTROGLIAL CONTROL OF EXCITATORY INTER-SYNAPTIC CROSSTALK IN THE BRAIN

Dmitri Rusakov

UCL Queen Square Institute of Neurology, University College London, UK

Extrasynaptic actions of the excitatory neurotransmitter glutamate are limited by high-affinity transporters expressed by perisynaptic astroglia. This helps maintain point-to-point transmission in excitatory circuits. Memory formation in the brain is associated with synaptic remodelling, but whether and how this affects perisynaptic astroglial processes (PAPs) and therefore extrasynaptic glutamate actions is poorly understood. We used a battery of advanced imaging methods, *in situ* and *in vivo*, to find that a classical synaptic memory mechanism, long-term potentiation (LTP), triggers withdrawal of PAPs from potentiated synapses. Optical glutamate sensors combined with patch-clamp and super-resolved 3D molecular localisation reveal that LTP induction in *ex vivo* brain slices thus prompts spatial retreat of astroglial glutamate transporters, boosting glutamate spillover and NMDA receptor-mediated inter-synaptic cross-talk. The LTP-triggered PAP withdrawal involves astroglial NKCC1 transporters and the actin-controlling protein cofilin but does not depend on major Ca2+-dependent cascades in astrocytes. We combine targeted viral transduction with multiplexed imaging *in vivo* to document a similar phenomenon under the physiological LTP paradigm (rhythmic whisker stimulation) in the intact brain. Our results thus uncover a mechanism by which a memory trace at one synapse could alter signal handling in multiple neighbouring connections by engaging use-dependent plasticity of local astroglia.

ASTROCYTE HETEROGENEITY AT SINGLE CELL LEVEL – PHYSIOLOGICAL AND DEVELOPMENTAL IMPLICATIONS

Mykhailo Batiuk

École Polytechnique Fédérale de Lausanne, Switzerland

Astrocytes, one of the major cell types in the CNS, perform a variety of roles crucial for brain physiology, neuronal function and synaptic transmission. Despite multiple functions, morphological variability, and distinct anatomical locations, decades-long assumptions stated that astrocytes are generally homogeneous cells. Although, this notion was often questioned in recent years.

To investigate the true extent of astrocyte molecular diversity across forebrain regions, we used single-cell RNA sequencing. Our analysis identified five transcriptionally distinct astrocyte subtypes in adult mouse cortex and hippocampus. *In situ* validation of our data revealed distinct spatial positioning of defined subtypes, reflecting the distribution of morphologically and physiologically distinct astrocyte populations. Our findings revealed the complexity of astrocyte heterogeneity, and hinted towards developmental and tissue micro-environment factors as possible bases of astrocyte heterogeneity.

FUNCTIONAL ROLES OF ASTROCYTE CALCIUM ELEVATIONS IN THE BASOLATERAL AMYGDALA

Olena Bukalo

National Institute on Alcohol Abuse and Alcoholism, NIH, USA

The ability to retrieve associations between environmental stimuli and previously encountered threat represents a fundamental form of memory crucial to survival. Recent studies suggest astrocytes support fear memory by modulating memory-encoding neural circuits and neuronal engrams in cortical and limbic regions. However, the precise mechanisms by which this occurs remain unknown. We monitored and manipulated astrocyte activity *in vivo* with fiber photometry in the basolateral amygdala (BLA), a brain region critical

to the formation, retrieval, and extinction of fear memories. First, our data demonstrate that population BLA astrocyte Ca2+ activity signals the retrieval of a cued threat memory then tracks the extinction-induced shift from a high to low fear state and subsequent return of high fear during context-driven renewal. Next, we found that genetic manipulations aimed to reduce Ca2+ activity in astrocytes impair formation/retrieval of fear memory. To further dissociate the significance of astrocytic Ca2+ signaling in fear memory, we employed a chemogenetic manipulation by expressing viral constructs for hM3D(Gq)- or hM4D(Gi)-coupled DREADD in BLA astrocytes. Systemic injection of the inert ligand clozapine n-oxide (CNO), prior to extinction training, have an opposite effect on freezing behavior. We found that freezing levels were markedly lower in hM3D-, but higher in hM4D-expressing animals as compared to mice expressing control viral construct, during early extinction trials, consistent with an impairment or improvement in fear memory retrieval. Using *in vivo* fiber photometry Ca2+ imaging during CNO application, we observed a different dynamic of Ca2+ signal in astrocytes in hM3D- and hM4D-expressing animals. Altogether, our data suggests that Ca2+ responses in astrocytes are not only tightly correlated with fear state, but also that BLA astrocyte Ca2+ activity is necessary for fear memory retrieval. Future studies will investigate how astrocytes are implicated in shaping neuronal networks in the amygdala during fear memory acquisition and retrieval.

Funding: Research supported by the NIAAA Intramural Research Program.

BIOLOGICAL SESSION 2

Basic Neuroscience

REGULATORY GENOMICS OF ASTROCYTE EVOLUTION

Ciuba K.[1], Piotrowska A.[1], Chaudhury D.[1], Dehingia B.[1], Dunski E.[1], Wójtowicz T.[2], Włodarczyk J.[2], Aleksandra Pękowska[1]

[1]Dioscuri Centre for Chromatin Biology and Epigenomics, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
[2]Laboratory of Cell Biophysics, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland

Astrocytes play an essential role in the maintenance of brain homeostasis. Virtually all neurological disorders are related to astrocyte dysfunctions. Remarkably, astrocytes have changed profoundly during the evolution of the mammalian brain. Human brains feature at least four morphotypes of astrocytes, while only one is present in the mouse brain. Furthermore, the evolution of primate astrocytes led to an enhanced complexity of protoplasmic astrocyte arborization. Recent transcriptomic comparisons of human, chimpanzee, and macaque cortical cells suggest that astrocytes might have evolved faster than neuronal cells. Molecular bases, as well as the functional significance of these changes, remain vastly unexplored. We used induced pluripotent stem cells to obtain human, chimpanzee, and macaque astrocytes *in vitro*. In my presentation, I will summarize our data highlighting the functional classes of genes significantly deregulated in human astrocytes compared to chimpanzees and macaque cells. I will discuss the relevance of these loci to human diseases. I will outline the gene and transcriptional regulatory network changes accompanying astrocyte evolution and give numerous examples of how human-specific enhancer elements might account for the differences in gene expression levels in cells of our species. I will discuss the epigenetic signature of promoter elements in astrocyte evolution. Our data will help better understand astrocytes' implications in brain evolution and shed new light on the link between human-specific gene expression and neurological disorders.

EVOLUTIONARY FEATURES OF HUMAN ASTROCYTES

Katarzyna Ciuba*, Aleksandra Piotrowska, Eryk Duński, Debadeep Chaudhury, Bondita Dehingia, Aleksandra Pękowska

Dioscuri Center for Chromatin Biology and Epigenomics, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland
**E-mail: k.ciuba@nencki.edu.pl*

Cognitive ability of human brain is exceptional comparing to other species, including non-human primates. However, its genetic basis remains one of the biggest unsolved questions of modern biology. To date, extensive research focused on neuronal cells. Yet, recent advancements in the field indicated the importance of astrocyte participation in regulation of neuronal plasticity and consequently cognitive processes. Importantly, astrocyte properties have changed remarkably throughout evolution. Human astrocytes are bigger and more complex than rodent ones, pointing to an evolutionary interplay between astrocyte properties and cognition. Nonetheless, genetic and functional determinants of astrocyte biology remain largely unknown.

To identify evolutionary changes, driving human-specific astrocyte expansion, we established an *in vitro* model of iAstrocytes (iPS-derived astrocytes) from distinct primate species (*H. sapiens, P. Troglodytes, M. Mulatta*). By combining molecular biolo-

gy, high-throughput genomics, including RNA-Seq, ATAC-Seq, ChIP-Seq, and bioinformatic methods, we identified genes and gene regulatory elements featuring differential activity between human and other primate species. We apply CRISPR/Cas9-based methods to examine function of particular, human specific, up- or down-regulated loci. This new data reveals human-specific genes and epigenetic regulatory networks. Consequently, our results will be instrumental for understanding the nature of the contribution of evolutionary changes in astrocyte epigenome and human specific brain functions.

Funding: Dioscuri Grant. Dioscuri is a program initiated by the Max Planck Society, managed jointly with the National Science Centre (Poland) and mutually funded by the Polish Ministry of Science and Higher Education and the German Federal Ministry of Education and Research.

CRISPR/CAS9-MEDIATED ABLATION OF FULL-LENGTH TCF7L2 ALTERS THALAMIC PHENOTYPE IN DEVELOPING MICE

Michael Gabriel*, Marcin Lipiec, Joanna Bem, Kacper Posyniak, Marta Wiśniewska

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The Wnt/β-catenin pathway is an evolutionarily conserved signalling pathway that regulates many biological processes during embryonic development. Transcription factor-7 like 2 (TCF7L2) is an effector of the Wnt/β-catenin signalling pathway that plays different roles in the development of the thalamus. We show that two groups of TCF7L2 isoforms are ubiquitously expressed in the thalamus at different developmental stages: the full-length (fl-TCF7L2) and truncated (dn-TCF7L2) isoforms. Although these isoforms differ respectively by the presence and absence of the β-catenin binding domain, studies have suggested that both of them act independently of β-catenin. The distinct roles of these isoforms in thalamic development remain enigmatic. We used CRISPR/Cas9 technology to specifically knockout fl-TCF7L2 by targeting exon 2. The expression of the dn-TCF7L2 isoform was preserved. We demonstrate that fl-TCF7L2 is vital for cell sorting and boundary formation during early thalamic development. We also show that fl-TCF7L2 regulates the expression of sub-regional thalamic markers highlighting its role in assigning thalamus-specific features to neurons. However, the fl-TCF7L2 knockout did not affect the guiding of thalamic axons into the ventral telencephalon. Overall, this study provides a robust understanding of the *in vivo* regulatory activities of fl-TCF7L2 on the development of the thalamus.

Funding: This project is supported by the National Science Centre in Poland (Grant No. UMO-2017/25/B/NZ3/01665).

MATHEMATICAL AND EXPERIMENTAL UNDERSTANDING OF THE MECHANISMS ASSOCIATED WITH THE FLUID EXCITABILITY AND FLIPPING OF MATURATING GRANULE CELLS

Danielewicz J.[1,2]*, Girier G.[2], Chizhov A.[3,4], Desroches M.[3], Encinas JM[1,5,6], Rodrigues S.[2,6]

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In response to prolonged depolarizing current steps, different classes of neurons display specific firing characteristics (i.e., excitability class), such as a regular train of action potentials with more or less adaptation, delayed responses, or bursting. In general, one or more specific ionic transmembrane currents underlie the different firing patterns. The intrinsic firing properties and ionic conductances in granule cells (GCs) are thought to reflect their developmental stage and maturation level. Among GCs, input resistance, threshold current, fluid excitability and the transition to depolarization block (DB) have been used as signatures of the degree of maturation and circuitry integration. Here we sought to investigate the influence of sodium and potassium channels conductances on DB in GCs with dynamic clamp – a computer controlled real-time closed-loop electrophysiological technique, which allows to couple mathematical models simulated in a computer with biological cells. We have observed that 44% of recorded cells exhibited what we have called a "flipping" behavior. Meaning, that these cells were able to overcome the DB and generate trains of action potentials at later current injections steps. We have develop a unified mathematical model of maturating GCs to explain fluid excitability, "flipping" and to capture the essential features of entry into DB.

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BIOLOGICAL SESSION 3

Neural substrates of affective behavior

WHOLE BRAIN MAPPING OF NEURONAL ENSEMBLES RESPONSIVE TO POSITIVE AND NEGATIVE STIMULI

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Many brain regions have been associated with positive and negative valence encoding, this is, the attribution of subjective value to sensory stimuli which determines subsequent appropriate behavior. Since dysfunction occurring in one or several of these brain regions is associated with mental disorders such as addiction or depression, it is essential to understand in detail what are all the components of this circuitry and what is their contribution for valence encoding. The main aim of this work was to perform a brain-wide identification of neuronal ensembles responsive to positive (cocaine) or negative (foothshock) valence stimuli. Taking advantage of permanent genetic access to transiently active neurons *via* TRAP, the recruited neuronal ensembles for valence-specific stimuli were quantified using a semi-automatized histological data analysis and generation of 3 dimensional models of the whole brain. Our data shows that brain regions of the reward circuit, such as the basolateral amygdala, the nucleus accumbens and the laterodorsal tegmental area, among other limbic and non-limbic regions, are particularly involved in positive and/or negative valence encoding. In conclusion, here we describe a brain-wide and region-specific involvement in valence encoding, with unprecedented detail.

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THE ROLE OF SOMATOSTATIN INTERNEURONS IN EMOTIONAL CONTAGION REGULATION

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To study how negative emotions are transferred in mice, particularly in the amygdala and prefrontal cortex, the Remote Transfer of Fear behavioral paradigm was employed. This involved housing pairs of mice (Observer and Demonstrator) for three weeks before the Demonstrator was removed from the home cage and subjected to adverse stimuli (10 foot shocks – 1s long, 0.6 mA). Once the Demonstrator had been returned to the home cage, the first ten minutes of interaction were recorded. After another eighty minutes, the mice were sacrified for immunohistochemical staining purposes. Sst-IRES-Cre mouse strains were used, as they expressed fluorescence marker (dTomato) through viral tagging. Combined with immunochemistry against c-Fos (a standard neuronal novelty marker), this enabled checking for somatostatin interneuron activity. The first ten minutes of interaction show higher levels of anogenital sniffing, body sniffing and self-grooming behavior for Observers (Control group). Meanwhile, exploratory behavior was higher for both Demonstrator and Observer mice (Experimental group). This altered behavior within the Experimental group, combined with increased neuronal activation (higher c-Fos levels for both amygdala and prefrontal cortex), confirms that emotional contagion occurred. Changes in somatostatin cell activity within amygdala region (Observers; both groups) likewise indicate their role in the emotional contagion regulatory circuit.

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THE ROLE OF THE CRF NEURONS IN THE CENTRAL AMYGDALA IN SOCIALLY TRANSFERRED FEAR

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The corticotropin-releasing factor (CRF) is a neuropeptide responsible for controlling stress respons-

es. The CRF-expressing neurons in the central amygdala (CeA) are activated by the social transfer of fear. We investigated the role of CRF neurons localized in the CeA in the remote threat paradigm, in which a non-stressed rat – the observer – is paired with a partner that experienced aversive foot-shocks (the demonstrator). We employed PSAM/PSEM chemogenetics to activate CRF neurons in male CRF-Cre observer rats. We analyzed observer rats' behaviors, including rearing, cage exploration, and social interactions, to explore the effect of CRF neurons stimulation on socially transfer fear. Activation of the CeA-CRF neurons decreased cage exploration and rearing in the observers paired with shocked demonstrators compared to the animals without blocking or paired with the control (non-shocked) demonstrators. Regardless of CRF blocking, the observers paired with the shocked demonstrators interacted with them longer than those paired with the non-shocked demonstrators. The data shows that activation of the CeA-CRF cells results in significant behavioral changes, which suggests a pivotal role of these neurons in socially transferred fear and emotional contagion.

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BACTERIAL-LIKE INFECTION DURING EARLY SYNAPTOGENESIS CHANGES PSYCHSOCIAL BEHAVIOR OF ADULT MICE

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Disorders that affect nervous system development are called neurodevelopmental disorders (NDDs). NDDs characterized by altered psychosocial behavior, such as autism spectrum disorder or schizophrenia are considered to have a multifactorial etiology. It is, however, believed that inflammatory reactions may be one of the causes.

The aim of this study was to evaluate changes in psychosocial behavior of adult mice treated with bacterial lipopolysaccharide (LPS) in early life. In terms of onset of exuberant synaptogenesis, postnatal day 7 (P7) in mice corresponds with the second trimester of pregnancy in humans. On P7, mice pups were injected either with LPS or physiological saline. After 3 weeks marble burying test, elevated plus maze, three chamber test, Eco-HAB® sociability test, and appetitive training in Intellicage were conducted. Mice after LPS treatment were less anxious and less active. The LPS-treated group spent more time together in the course of the social test. Interestingly, males avoided social stimulus from unknown animals, whilst females were more interested in social stimulus than the control group. Additionally, animals injected with LPS needed more time to learn new conditions. Therefore presented results suggest, that immune activation during neurodevelopment induces alterations of behavior that resemble symptoms observed in human NDD patients.

COMPLEXITY OF THE MIDBRAIN INTERPEDUNCULAR NUCLEUS INNERVATION BY THE BRAINSTEM NUCLEUS INCERTUS – POTENTIAL INVOLVEMENT IN NOVELTY PREFERENCE

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Correct response to novel stimuli is crucial for animals to adapt to ever-changing environment, and such responsiveness is disrupted in many neuropsychiatric diseases. One of the key nodes in familiarity signalling and expression of novelty preference is midbrain interpeduncular nucleus (IPN). IPN is strongly innervated by nucleus incertus (NI), a highly stress sensitive component of an ascending arousal network. However, the nature of the NI-IPN interactions remains largely unknown. We showed that the NI innervation of IPN is predominantly monosynaptic, using intra NI injections of viral vectors carrying channelrhodopsin-2 and YFP male rats, leading to expression fluorescence protein. During whole-cell patch-clamp *ex vivo* experiments electrical activity of IPN neurons was recorded, while NI originating fibers were optically stimulated. Both outward and inward light-evoked postsynaptic currents (le-PSCs) were observed. Inward le-PSCs were blocked by glutamate receptors antagonists whereas outward le-PSCs were inhibited by GABAA receptor antagonist, what confirmed their glutamatergic and GABA-ergic nature, respectively. Interestingly, we observed IPN neurons, that had both excitatory and inhibitory inputs from NI, as well as those, which were innervated directly and indirectly by NI. Our data show that the NI-IPN axis may constitute an important neuronal element involved in adapting novelty preference to stressful conditions.

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BIOLOGICAL SESSION 4

Markers of Aging

Symposium organizer: Dominika Drulis-Fajdasz
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CIRCULATING MICRORNAS AS EARLY BIOMARKERS IN ALZHEIMER'S AND OTHER AGING-RELATED DISEASES

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Circulating miRNAs in blood plasma present significant potential for use as presently unavailable minimally-invasive biomarkers for diagnosis of aging-related diseases, such as cancer or Alzheimer's disease (AD). Recently we identified a panel of 6 dysregulated miRNAs in blood plasma of patients with early AD (Patent EP3449009). Here we applied RT-qPCR, the most sensitive and inexpensive analysis method of circulating miRNA, for verification studies in a new cohort of 50 AD patients and 50 healthy control subjects. As current methods of identifying optimal normalisers are lacking in their evaluation of the stability of normalizers in aging population, we created a novel, transparent, method for selecting optimal normalisers in aging population. The obtained data showed significant differences for all tested panel miRNAs in their plasma levels in AD patients, confirming chosen miRNAs as minimally-invasive diagnostic biomarkers for AD. Moreover, we recommend the standard protocol for assessment of plasma miRNA levels in an aging population employing a novel set of normalizers.

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MONITORING METABOLITE PROFILES DEPENDING ON AGING PROCESSES – METABOLOMICS APPROACHES

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The phenomenon of used metabolomics approaches, especially nuclear magnetic resonance (NMR) spectroscopy, is not only about identification and quantification of all metabolites in biological samples, but also allows visualization of the actual metabolic state of living organisms studied at a particular point in time. This unique feature distinguishes metabolomics from other omics studies like genomic, transcriptomic, and proteomics. It is generally known that the metabolic coupling of astrocytes and neurons plays a key role in the phenomenon of plasticity of neural networks and the formation of memory tracks. Use of NMR method to analyze the image of the physiology of nervous tissue at different ages is quite attractive and the observed changes between chosen metabolites, in compared animal groups, may give new information about changes in cognitive abilities and the formation of new memory traces implicated with age.

WESTERN DIET AS A TRIGGER OF ALZHEIMER'S DISEASE: FROM METABOLIC SYNDROME TO NEURODEGENERATION

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An excess of saturated fatty acids and simple sugars in the diet is a known environmental risk factor of Alzheimer's disease (AD) but the holistic view of the interacting processes through which such diet may contribute to AD pathogenesis is missing. This presentation will provide an overview of the evidence demonstrating that WD-associated systemic alterations drive impairment of the blood-brain barrier (BBB) and development of neuroinflammation paralleled by accumulation of toxic amyloid. Later these changes are followed by dysfunction of synaptic transmission, neurodegeneration and finally memory and cognitive impairment. The mounting results indicate that WD can trigger AD by acceleration of inflammaging, and that BBB impairment induced by metabolic and systemic inflammation play the central role in this process. This overview of the sequential, complex pathomechanisms initiated by WD, which can lead from peripheral disturbances to neurodegeneration, can support future prevention strategies.

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SENOLYTIC TREATMENT CHANGES AGE-ASSOCIATED COGNITIVE DECLINE AND ELEVATED PERIPHERAL INFLAMMATION IN AGED BUT NOT YOUNG MALE WISTAR RATS

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Aging is associated with cognitive decline and accumulation of senescent cells which could be targeted by senolytics such as Dasatinib and Quercetin (D+Q). We studied the effect of senolytics on multifactorial aging-related cognitive dysfunctions by testing male Wistar rats in the active allothetic place avoidance task. Our studies revealed that 8 week-long treatment with D+Q decreased peripheral inflammation measured by the levels of serum inflammatory mediators (including SASP factors) in aged rats which coincided with long lasting (at least 6 weeks) alleviation of learning deficits and memory impairments observed in aged animals. We also observed changes in the dendritic spine morphology of the apical dendritic tree from the hippocampal CA1 neurons upon D+Q treatment and changes in the trimethylation level of histone H3 isolated from the hippocampus. Our results support the notion that senolytics on alleviating age-associated cognitive dysfunctions.

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BIOLOGICAL SESSION 5

Advanced neurotechnologies for brain activity monitoring and modulation

Symposium organizer: Richárd Fiáth (*Research Centre for Natural Sciences, Budapest, Hungary*)

EVOLUTION OF SILICON-BASED PROBES DEVELOPED FOR LARGE-SCALE NEURONAL RECORDINGS

Richárd Fiáth

Research Centre for Natural Sciences, Budapest, Hungary

Penetrating neural probes were developed with the intention to record or to modulate the electrical activity of neurons located close to the implanted probe shank. First planar silicon-based devices designed for *in vivo* experiments contained only a few recording sites on a single shank monitoring the activity of a limited number of neurons, while the current technology used to fabricate state-of-the-art silicon probes allows the placement of over a thousand recording sites on a single or on multiple silicon shanks. This impressive engineering achievement was accomplished by the application of complementary metal-oxide-semiconductor (CMOS) technology which also resulted in a remarkable increase in the spatial resolution of these *in vivo* recordings. The resulting high-density, high-channel-count measurements usually contain the extracellular electrical activity of hundreds of neurons obtained simultaneously from multiple brain areas. This lecture gives a brief overview of the history of silicon-based neural probes, introduces their main features and highlights the main applications of these tools.

APPLICATION OF HIGH-DENSITY NEURAL PROBES TO EXPLORE THE COMPLEX SPATIOTEMPORAL DYNAMICS OF THALAMOCORTICAL ACTIVITY

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The application of recent developments in complementary metal-oxide semiconductor (CMOS) technology in invasive extracellular devices has led to innovative neural probes with an increased channel count and spatial resolution. These novel devices provide an opportunity to capture a much more detailed picture of the complex spatiotemporal dynamics of neuronal activity both at the cellular and network level. To demonstrate this, on the one hand, we present a large, publicly available dataset of extracellularly recorded single neurons (n=7126) obtained with a high-density single-shank silicon-based probe from the neocortex of anesthetized rats. Our preliminary findings indicate that spatial features extracted from the recorded high-resolution spike waveforms might aid a more reliable identification of cortical cell types. On the other hand, we used Neuropixels silicon probes to map thalamic activity of anesthetized rodents to lo-

cate propagating patterns of spiking activity during the active states of slow waves and to investigate their spatiotemporal features.

TRANSPARENT MICROECOGS FOR MULTIMODAL NEUROIMAGING

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Multimodal measurements have emerged as both functional and structural observation of the brain is required to understand the complex mechanism of neuronal ensembles. Electrophysiology is still used as a gold standard to interrogate brain activity, however, the advent of new optical characterization tools like optogenetics, calcium imaging, or voltage-sensitive dye imaging catalyzed the development of transparent neural interfaces that enable the application of both modalities. This talk will summarize recent results of our group that relied on the application of transparent microelectrocorticography arrays in conjuction with intrinsic optical imaging and calcium imaging in anaesthetized and awake mice and cats. Specifically, optical and electrical performance of polyimide/indium-tin oxide, Parylene HT/indium-tin-oxide and thiol/ene-acrylate/gold electrodes will be demonstrated in multimodal neuroimaging experiments.

COMPACT OPTRODE FOR *IN VIVO* OPSIN DELIVERY, OPTICAL STIMULATION AND ELECTROPHYSIOLOGICAL RECORDINGS IN FREELY BEHAVING ANIMALS

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We present a multifunctional optrode that combines a silicon-based neural probe with an integrated microfluidic channel, and an optical glass fiber in a compact assembly. The tapered silicon probe has a maximum cross-section of 50 µm × 150 µm, and comprises an 11-µm-wide buried fluidic channel and 32 recording electrodes (diameter 30 µm). We applied the optrode to inject a viral vector carrying a ChR2-construct in the prefrontal cortex and subsequently photostimulated the transduced neurons for up to 9 weeks post-implantation in a freely moving rat. In addition, we simultaneously recorded neural activity from both the target and the adjacent regions. We observed minimal inflammation surrounding the recording shank and the electrophysiological recording quality was stable over time. With a total system weight of 0.97 g, our multifunctional optrode enables precise local injection and high spatial specificity while minimizing tissue damage.

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BIOLOGICAL SESSION 6

Systems Neuroscience of Sensory Processing

THE DEVELOPMENT OF CIRCUITS AND COMPUTATIONS FOR NAVIGATION AND MEMORY

Flavio Donato

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The entorhinal-hippocampal network contributes to the formation of episodic memories by creating an internal representation of the environment where experience unfolds. Such internal representation, or cognitive map, is instantiated in the activity of several functionally-specific cell types whose activity is modulated by space. Among these cell types, we distinguish neurons that are active at one or more specific locations in the environment (place and grid cells), or next to borders (border cells), or when the animal faces specific directions (head-direction cells). In rodents, while the firing properties of head-direction and border cells are adult-like at the onset of spatial exploration, spatial tuning in grid and place cells emerges and is refined progressively during the first months of life. This maturation process might depend on the

establishment of specific connectivity motifs between the entorhinal cortex and the hippocampus. In fact, we previously showed that the functional maturation of such cell types is accompanied by the structural maturation of the entorhinal-hippocampal circuit, which is driven by an activity-dependent instructive signal that instructs the stepwise maturation of excitatory and inhibitory neurons at each stage of the network. Here, we will discuss recent studies whose aim is to understand how the emergence of spatial tuning in the developing entorhinal-hippocampal network shapes learning and memory processes during early postnatal life. Furthermore, we propose that studying the functional ontogenesis of the brain's representation of space offers a unique opportunity to understand the contribution of individual cell types to hippocampal computations, and to dissect the contribution of such computations to learning and memory processes at multiple stages of an animal's life.

SIMPLIFIED APPROACH TO ANALYZE DATA FROM AUTOMATED T-MAZE AND TO CHARACTERIZE BEHAVIOR WITH DEEP LEARNING

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Behavioral experiments are a desirable tool in neuroscience but they can suffer from various factors, which influence reliability and reproducibility. Automatization of the process can overcome limitations such as experimentator input or data collection, and can help to reduce bias. With an emergence of machine learning and deep neural networks in recent years, it is possible to standardize behavioral studies and produce high quality data sets.

In this study we present automated t-maze system, in which mice learn to acquire a reward, based on two separate visual cues. System uses Bonsai software and Arduino with mechanical components, to record and to train animals with predefined protocol. After reaching appropriate threshold of correct choices, mice were subsequently tested in the same protocol with only one set of visual cues. DeepLabCut software was used for pose estimation and further analysis of mice trajectories. Furthermore, successful pose estimation in T-maze jumpstarted analysis of animal behavior in the open field and adaptation to known concept of social boxes.

Results from T-maze showed significant differences between pre-trained and trained animals, both in performance-oriented and trajectory-oriented manner. Automatization and deep learning allowed for a degree of analysis that was hard to achieve before and highlighted small details that would pass unnoticed otherwise. These tools are becoming mandatory for our future studies for efficient parametrization of social behavior.

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PLASTICITY OF TEMPORAL INTEGRATION IN FERRET AUDITORY CORTEX

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Retrieving meaning from complex auditory stimuli requires flexible binding in time of auditory features at different timescales. Recent reports suggest that auditory perception relies on a hierarchy of auditory timescales and progressive processing of information through a hierarchy of cortical areas. Although temporal dynamics of auditory perception have been thoroughly studied, little is known about the plasticity of temporal integration windows (or timescales) in the auditory cortex. To address this question we study the neural responses of the auditory cortex of the ferret to complex continuous auditory stimuli across a range of behavioral states. First, we assess the similarity of the gradient of sensory timescales in the auditory cortex of the ferret to that of the human. Subsequently, we address the question of plasticity by comparing the structure of this gradient across different behavioral states. Finally, we explore other sources of variability such as the internal state of the animal by relating the structure of the gradient to the physiological state of the animal. This work provides insights into the cortical mechanisms underlying flexible auditory performance at multiple scales.

MEMORIES IN INHIBITORY NEURONS – A COMPUTATIONAL MODEL FOR MEMORY STORAGE AND RECALL USING INHIBITORY PLASTICITY

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Information in the brain is usually thought to be transmitted mainly *via* excitatory neurons, while local inhibitory circuits are considered to merely stabilize excitation. As such, in most network models, more attention is given to excitatory population dynamics, relegating inhibition to a support role. However, numerous studies highlight the functional importance of inhibitory neurons beyond stabilization, such as regulation of information transfer or memory processes.

Here, we explore the role of inhibitory-to-inhibitory plasticity as a mechanism to produce network models with plausible inhibitory dynamics. To study the interaction between the classical role of inhibition – stabilizing excitation – and other possible inhibition-specific roles, we analyze the behavior of a recurrent spiking network simulated with a plasticity rule similar to Vogels et al., 2011 on the inhibitory-to-inhibitory and inhibitory-to-excitatory connections.

We find that, depending on the firing rate of the inhibitory population, the network activity can be silenced, highly synchronized, or bi-stable. We propose conditions on network and plasticity parameters to enable inhibition to have its own rich dynamics while still stabilizing excitation. Overall, our study shifts the focus from excitatory to inhibitory dynamics in plastic network models to better account for the profuse inhibitory dynamics observed experimentally.

CELLULAR AND MOLECULAR FOUNDATIONS OF HAIR FOLLICLE NOCICEPTION

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Hair follicle innervation forms an elaborate sensory apparatus that provides information on even the most delicate hair movements. As a measure of protecting the pelage, hair pulling evokes sharp pain sensation. We decided to investigate the neural encoding and molecular mechanisms underpinning this unique painful modality. We first examined mechanotransduction mechanism and found that patients with PIEZO2 deficiency syndrome do not feel hair pull pain, indicating for the first time the role of PIEZO2 in acute pain. Subsequently, we established that a PIEZO2-positive class of sensory neurons present in primates is homologous to murine hair pull nociceptors. Therefore, to study neuronal coding, we used *in vivo* imaging in mice to show that a subset of hair-pull responding neurons shows specificity and selective tuning. Consistently, we observed diminished responses to low pull forces in PIEZO2-KO neurons which was in line with measured hair nociceptors activation thresholds. To test functional conservation of hair pull nociceptors we performed human microneurography and demonstrated that hair pull pain is indeed coded by a dedicated novel group of Aβ fibers. In conclusion, we show that hair pull pain is a PIEZO2-dependent sensation conveyed by an evolutionarily conserved labelled line of fast conducting low-threshold nociceptors.

BIOLOGICAL SESSION 7

Hypothalamic control of behavior

UNDERSTANDING THE NEURAL CIRCUITS OF STRESS EATING

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Stress can enhance cravings for palatable food (e.g., fat and sugar) and can also increase impulsive behavior. In vulnerable individuals these effects contribute to binge eating and obesity. The neurobiology underlying stress eating remains largely unclear, however our lab seeks to understand how stress alters neural circuit function to increase the pursuit of palatable foods. In particular we focus on how stress alters communication within cortical-hypothalamic-(meso)limbic networks. We assess the stress-altered functioning of such circuitry using a combination of *ex vivo* techniques (in particular patch-clamp slice electrophysiology) combined with various *in vivo* approaches (behavioral assays during neural circuit monitoring/manipulation techniques). With these approaches we strive to provide multi-level insight in the neurobiological mechanisms of stress eating responses.

ROLE OF AGRP/NPY NEURONS IN DEVELOPMENT OF THE OBESITY PHENOTYPE ON THE MOUSE MODEL WITH INDUCED DELETION OF THE *DICER1* GENE

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Food is the foundation of the survival pyramid while hunger is the primary motivator of the search for and acquisition of nourishment. The brain is the locus of superior centers involved in hunger and satiety regulation. The arcuate nucleus located in the hypothalamus is the primary first-order center processing the body's energy status information. Said structure's functional division includes two populations of opposing neurons: AgRP/NPY, which stimulates food intake, and POMC/CART, responsible for promoting satiety and appetite suppression. Any disturbances within the arcuate nucleus may lead to changes in eating behavior and development of metabolic diseases such as obesity.

Neurospecific deletion of the *Dicer1* gene, which leads to massive microRNA loss, is an example of such impairment. This mutation promotes obesity development linked to increased food intake. Here, this phenomenon is described in relation to orexigenic AgRP/NPY neurons. The microRNA-loss-dependent obesity is established through study of selected transgenic animal models and use of sophisticated genome editing tools.

CHANGES IN THE DORSOMEDIAL HYPOTHALAMIC HORMONAL RESPONSES AND BASAL ACTIVITY IN HIGH-FAT DIET FED RATS UNDER FEEDING RESTRICTION

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The dorsomedial hypothalamus (DMH) is a part of the food-entrainable oscillator regulating circadian periods of feeding and drinking, as well as energy expenditure. Our previous research presented differences in the DMH activity between rats under control (CD) and high-fat diet (HFD). HFD group characterised by additional feeding during daytime, therefore their non-active phase. Following that study, we decided to use a similar protocol modified by applying a feeding restriction, allowing the animals to feed only during their physiological period of behavioral activity. This allowed us to observe whether the disruption seen in the DMH activity in HFD group is purely the result of a modified diet or if it originates from animals' feeding behavior instead. Using data obtained with immunohistochemical and electrophysiological methods we analysed if aforementioned changes in the DMH activity also occur after night-feeding only. *Ex vivo* multi-electrode array recordings (MEA) also allowed us to compare the DMH neuronal activity after applying 3 pivotal satiety hormones: oxyntomodulin (OXM), glucagon-like peptide 2 (Glp2) and exendin-4 (Exn4). We compared its responses not only between the CD and HFD groups but also between day and night. This research proposes restricted feeding to prevent HFD induced disruptions in the DMH activity and presents its responses to satiety hormones.

OXYTOCIN SIGNALLING IN THE BRAINSTEM NUCLEUS INCERTUS MODULATES AROUSAL RELATED BEHAVIORS

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Oxytocin (OT)/oxytocin receptor (OTR) signalling modulates food/water intake, reproduction, memory, emotional processing, and social interaction among others. A possible effector of these actions are the OTR-expressing neurons in the nucleus incertus (NI) that modulate arousal and other processes that overlap with known OT functions. Therefore, our aim was to characterise the anatomy, neuronal and behavioral effects of OT/OTR signalling in the rat NI.

In these studies, we employed *in situ* hybridisation, immunostaining, viral tract-tracing, and electrophysiological *ex vivo*. Finally, using a newly generated OTR-IRES-Cre knock-in rat, we chemogenetically activated NI OTR-expressing neurons and examined the effects on behavior.

A majority of OTR mRNA-positive NI neurons are GABAergic. OT dose- and OTR-dependently excited

70% of NI neurons. The NI lacks a substantial OT innervation, but the juxtaposition to the fourth ventricle suggests endogenous OT may reach the NI *via* the cerebrospinal fluid. Chemogenetic activation of OTR NI neurons promoted locomotor activity, reduced anxiety, altered social interaction, and improved social recognition. These studies identify the brainstem nucleus incertus as a site of action of OT/OTR signalling. Notably, our results reveal a possible neuronal mechanism underlying OT-mediated modulation of arousal, and provide evidence for a key role of extrahypothalamic OT actions in governing behavior.

Funding: Alexander von Humboldt Foundation, Germany: Humboldt Research Fellowship; NSC, Poland: UMO-2018/30/E/NZ4/00687.

BIOLOGICAL SESSION 8

Mitochondrial dysfunctions in neurological disorders

Symposium organizer: Agnieszka Krzyżosiak (*The Group of Astrocyte Biology, Life Sciences & Biotechnology Center, Łukasiewicz Research Network – PORT Polish Center for Technology Development, Wrocław, Poland*)

DRUG DISCOVERY OF MITOCHONDRIAL DISEASES USING PATIENT-SPECIFIC BRAIN ORGANOIDS

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Metabolism is essential for providing the energy necessary to ensure proper cellular function. Mutations in genes regulating this process lead to inherited metabolic disorders that can be organ-specific or multi-organs. Neonatal screenings can identify the presence of a metabolic disorder. However, therapeutic opportunities are only available for a small number of these disorders. Among incurable inherited metabolic diseases, mitochondrial diseases represent a major therapeutic challenges, given that they can be caused by mutations in oxidative phosphorylation genes that are encoded by either the mitochondrial DNA (mtDNA) or the nuclear DNA (nDNA). This fact hampers the generation of effective model systems, given the challenges associated with mtDNA engineering.

In this talk, I will first summarize how stem cell metabolism has emerged as a key aspect associated with the modulation of cell fate transition. I will then present our efforts in using patient-derived induced pluripotent stem cells (iPSCs) to study mitochondrial diseases. We focus primarily on Leigh syndrome, which is the most frequent and most severe mitochondrial disease affecting 1/40,000 newborns. We show that neuronal cultures and brain organoids derived from Leigh syndrome iPSCs can be used as model systems to investigate the disease mechanisms and to carry out phenotypic compound screenings. Our data pave the way to the identification of disease-modifying therapies for currently incurable mitochondrial disorders.

SINGLE-CELL ANALYSIS OF A-SYNUCLEIN-INDUCED MITOCHONDRIAL DYSFUNCTION *IN-VIVO*

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Parkinson's disease (PD) is characterised by progressive degeneration of dopaminergic cells in the substantia nigra (SN) and is also linked to the accumulation and aggregation of α-synuclein. Clinical and experimental evidence supports a vital role for mitochondrial dysfunction in the pathogenesis of both familial and sporadic PD. Our aim was to develop a quantitative assessment of potential mitochondrial abnormalities at the single-cell level in a mouse model of α-synuclein overexpression. AAVs encoding for human α-synuclein were injected into the SN and after 4 and 12 weeks, immunofluorescent staining revealed that sustained exposure to α-synuclein is associated with a loss of mitochondrial complex I/IV, within dopaminergic neurons. Complex I appears to be more negatively affected than complex IV. Furthermore, our results also indicate that a decreased complex I: Total mitochondria ratio is inversely correlated with the intraneuronal levels of α-synuclein, with this inverse correlation becoming more pronounced at the later timepoint.

Funding: Alexander von Humboldt society, DZNE and the Innovative Medicines Initiative 2 (PDmitoQuant consortium).

ALTERED ULTRASTRUCTURE OF SYNAPTIC MITOCHONDRIA IN FRAGILE X SYNDROME LINKED WITH METABOLIC CHANGES

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In the synapse, an important pool of mitochondrial proteins is translated locally on the bases of mR-

NAs transported from cell soma. Moreover, the local synthesis of proteins constituting mitochondrial respiratory chain complexes is increased by synaptic stimulation. In Fmr1 KO mice, a mouse model of fragile X syndrome, proteomic analysis shows dysregulated levels of mitochondrial proteins. Mitochondrial functions are fundamentally linked to their morphology and inner membrane ultrastructure. We used Serial Block Face-Scanning Electron Microscopy (SBF-SEM) to analyze mitochondrial ultrastructure in the hippocampi of Fmr1 knock-out (KO) and wild-type (WT) male mice. Mitochondria shapes and volumes were reconstructed with the use of RECONSTRUCT software. We compared the morphology and the number of synaptic mitochondria in Fmr1 KO and WT mice. To understand this genetic mutation's physiological consequences for mitochondrial function in the synapse, we measured the level of reactive oxygen species (ROS) and ATP in mice of three different ages. We found a significant decrease in mitochondrial ROS levels in 13 weeks old Fmr1 KO mice compared to WT mice.

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BEHAVIORAL AND BIOENERGETIC EFFECTS FOLLOWING CHRONIC ACEA TREATMENT IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Different brain mechanisms have been associated with the pathophysiology of Alzheimer's disease (AD) including disrupted bioenergetic processes (i.e., mitochondrial dysfunction) and alterations of different components of the endocannabinoid system (ECS). The ECS is considered a key modulator of many brain and body functions, such as cognitive and metabolic processes. Since both, the ECS and brain bioenergetics, have emerged as a potential therapeutic target in AD, we aimed to explore the link between cannabinoids, bioenergetics, and AD. Thus, we conducted a comprehensive sex- and age-dependent behavioral characterization (memory function, social-related behaviors, depressive- and anxiety-like states) in the APP/PS1 mouse AD model after chronic treatment with the CB1 receptor agonist ACEA at 3 months of age (pre-symptomatic stage). Male APP/PS1 mice exhibited a cognitive decline in long-term recognition memory (assessed in the Novel Object Recognition task) that was reversed with the ACEA treatment. In contrast, female APP/PS1 mice showed significant deficits in associative learning (evaluated through a contextual fear conditioning task). Furthermore, we found sex- and brain region-dependent alterations in ECS components and related bioenergetic processes (i.e., OXPHOS, Krebs cycle pathway). Overall, this study sheds light on the relationship between cannabinoids, bioenergetics, and AD demonstrating that cannabinoid drugs might be a promising therapeutic approach for AD.

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BIOLOGICAL SESSION 9

Blood-brain barrier

Symposium organizer: Aleksandra Rutkowska (*Medical University of Gdańsk, Poland*)

THE HUMAN BLOOD-BRAIN BARRIER SPHEROIDS AS A MODEL FOR STUDYING MULTIPLE SCLEROSIS PATHOPHYSIOLOGY

Aleksandra Rutkowska

Medical University of Gdańsk, Poland

The *in vitro* blood-brain barrier (BBB) models were initially built on a membrane in a transwell system with a single cell type, usually the brain vascular pericytes or endothelial cells (ECs). Recently, several advances have been made to build more sophisticated and physiologically relevant *in vitro* models of the BBB. Here, we present a tri-cell BBB model comprised of conditionally immortalised human brain microvascular ECs, pericytes and astrocytes. The cells are seeded in the classical transwell system or can be grown into a 3D spheroid. In a transwell or spheroid form, the model can be applied to study drug BBB permeability, disruption or breakdown of the BBB, transmigration of the immune cells, and many others. We use these models to study the pathophysiology of the BBB in multiple sclerosis and, in particular, the mechanisms involved in the disruption of the BBB, its protection and recovery. Both, the transwell and spheroid models, can also be used to measure the transmigration of immune cells. We measure the chemotaxis of CD4+ cells isolated from multiple sclerosis patients and modulate their function in

the search for novel therapy. Here, we present some of our preliminary results obtained with these BBB models and discuss the shortcomings and challenges ahead.

EBI2 RECEPTOR-MEDIATED REGULATION OF IMMUNE CELL TRANSMIGRATION *VIA* AN *IN VITRO* TRI-CELL MODEL OF THE BLOOD-BRAIN BARRIER

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Multiple sclerosis (MS) is a chronic, progressive, neuroinflammatory and neurodegenerative disease characterised by the entry of peripheral immune cells into the central nervous system *via* a damaged blood-brain barrier (BBB). The infiltrating immune cells propagate the inflammatory signalling and attack the myelin sheaths surrounding the neuronal axons, leading to their neurodegeneration and death. Oxysterol 7α,25OHC is a natural ligand for the Epstein-Barr virus-induced receptor 2 (EBI2, GPR183) which, among other functions, regulates immune cell migration. Using a human *in vitro* BBB spheroid model, comprised of endothelial cells, pericytes and astrocytes, we characterised the expression of EBI2 and EBI2-related enzymes after inflammatory stimuli in the cells forming the BBB. We also looked at the integrity of the BBB after stimulation with human cerebrospinal fluid and serum collected from healthy and MS patients. Finally, we investigated the migration of immune cells *via* opened BBB.

BENEFICIAL EFFECTS OF AP39 – A NEW HYDROGEN SULFIDE DONOR – ON MITOCHONDRIAL FUNCTIONAL PARAMETERS AND BLOOD-BRAIN BARRIER INTEGRITY IN A RAT MODEL OF BRAIN ISCHEMIA

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Ischemic stroke is one of the leading cause of death and disability worldwide. Some evidence highlights the beneficial properties of hydrogen sulfide (H2S) donors in animal models of brain ischemia, but these data are inconclusive. This study was undertaken to verify the neuroprotective effects of AP39 – a novel molecule that releases H2S in the mitochondrial space of neural cells. For this purpose, a model of 90-minutes middle cerebral artery occlusion (MCAO) in a rat was performed along with the techniques of neurological deficit and infarct volume assessment. AP39 (100 nmol/kg, i.v.) was administered 10 minutes after reperfusion. Using the Seahorse XF analyzer, the functional parameters of the isolated mitochondria (efficiency of the oxidative phosphorylation and glycolysis) from frontal cortex and dorsal striatum were determined. Next, the integrity of the blood-brain barrier (BBB) was assessed. AP39 resulted in a reduction in the infarct volume and neurological deficit. The modulating effect of AP39 on the oxygen consumption rate and the level of glycolysis has been demonstrated. AP39 showed its protective potential on the BBB integrity. Results indicate that AP39 may have a beneficial effect in ischemic diseases, however, further work on the molecular mechanism of its action is necessary.

THE INFLUENCE OF HYPERCHOLESTEROLEMIA ON THE STRUCTURE OF THE VASCULAR WALL AND THE FUNCTION OF THE BLOOD-BRAIN BARRIER

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The most important consequence of hypercholesterolemia is increased BBB permeability, resulting from changes in the level of protein synthesis and distribution in the basal membrane of the cerebral vessel wall. This leads to a disturbance in the flow of metabolites of the cholesterol synthesis pathway through the wall of the cerebral vessels, which may intensify inflammatory and neurodegenerative processes. Among many vascular wall proteins and associated enzymes, agrin (Agr), matrix metalloproteinase-9 (MMP9), and aquaporin-4 (AQP4) may be of importance.

We analyzed the level of vascular wall proteins Agr, MMP9, and AQP4 by performing immunohistochemical staining and BBB permeability changes using labeled fluorescein isothiocyanate–dextran. The study included the prefrontal cortex, motor cor-

tex, hippocampus, and striatum in 3-month-old and 12-month-old mice in the C57/BL6 control and the LDLR-/-/ApoE-/- „knock-out" group. The present study showed that both the development of hypercholesterolemia, the age of the mice studied, and the location of the lesions in the brain had an impact on BBB function. Differences in the content of proteins responsible for maintaining the integrity of functional barrier systems have a significant impact on BBB permeability, especially in younger mice. The development of the vascular system that occurs with age may limit the effects of these disorders and seal the BBB.

COGNITIVE SESSION 1

How does exercise benefit cognition and emotion?

Symposium organizer: Tomasz S. Ligeza
(*Psychophysiology Laboratory, Jagiellonian University in Krakow, Poland*)

THE ROLE OF PHYSICAL FITNESS ON BRAIN STRUCTURE AND FUNCTION DURING CHILDHOOD

Irene Esteban-Cornejo
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Using data from a Spanish study of children with overweight/obesity (i.e., ActiveBrains Project), we examined how different components of physical fitness (i.e., cardiorespiratory fitness, motor fitness and muscular strength) associate with brain structure (global and regional gray matter volume, surface and cortical thickness, global and regional white matter volume, and global and regional white matter microstructure) and brain function (hippocampal functional connectivity), and whether these associations had academic implications.

Our findings highlight physical fitness components seem to selectively influence brain structure and function, coupled with academic implications in children with overweight/obesity. Specifically, cardiorespiratory and motor fitness were associated with greater gray matter tissue of numerous cortical and subcortical brain structures, and better hippocampal functional connectivity; however, muscular strength seems to be the fitness component more susceptible and selective to influence white matter, but not gray matter indicators. This presentation will guide future studies on fitness and brain health during childhood.

EXERCISE AND MOOD: INSIGHTS INTO BRAIN MECHANISMS OF THE RELATIONSHIP WITH THE USE OF EEG/MEG METHODS

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This presentation will continue the considerations of possible brain mechanisms in which exercise improves mood. The main focus will be on exercise-induced changes in the processing of emotional stimuli and abilities to control emotions after exercise and across people of different physical activity levels. The presented brain outputs are acquired using EEG/MEG measures and concern healthy and depressed young adults. Positive changes in the brain's response to emotional stimuli, as well as changes in effective connectivity patterns across structures involved in mood regulation, will be proposed as possible mechanisms in which exercise benefits mood.

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THE ASSOCIATIONS BETWEEN ACCELEROMETER-MEASURED SEDENTARY TIME, BEHAVIORAL AND NEUROFUNCTIONAL CORRELATES OF COGNITIVE CONTROL IN YOUNG AND MIDDLE-AGED ADULTS

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Epidemiological evidence suggests that sedentary behaviors (e.g., TV viewing, driving) may contribute to poorer cognitive control. However, the relationships be-

tween sensor-measured sedentary behavior duration, cognitive control, and its neurofunctional correlates remain poorly understood. We will present evidence on the associations between accelerometer-measured sedentary time (ST), behavioral and neurofunctional correlates of cognitive control in two populations of young and middle-aged adults. We will discuss opposing associations between ST and susceptibility to resistance to framing (a correlate of cognitive control) in young, aerobically fit adults using the baseline data from the INSIGHT trial (NCT02780739). We will show how functional connectivity of the dorsal attention network at rest, measured with functional magnetic resonance imaging, may contribute to these relationships. Second, we will present evidence suggesting that ST may contribute to inhibitory control deficits in young and middle-aged adults with overweight and obesity using baseline data from Persea Americana for total health trial (NCT02740439). We will complement our behavioral findings with neuroelectric results (event-related brain potentials), suggesting attenuated neural efficiency with higher ST in adults with overweight and obesity. The presented findings will highlight potential behavioral and neurofunctional pathways that may contribute to decreased cognitive performance in sedentary young and middle-aged individuals.

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UNRAVELING NEURAL MECHANISMS UNDERLYING EXERCISE-MOOD RELATIONSHIPS IN YOUNG HEALTHY ADULTS USING MAGNETIC RESONANCE IMAGING (MRI)

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While it has already been shown that exercise can have beneficial effects on mood and even symptoms of psychiatric disorders, we are still in the early stages of understanding which neural mechanisms drive these effects. Therefore, investigating acute and long-term exercise interventions on affective processing using modern imaging techniques like magnetic resonance imaging (MRI) may be particularly fruitfull for unraveling the neural mechanisms underlying exercise-induced affective changes. An overview will be provided of acute and long-term exercise intervention studies using structural and functional (task-based and resting-state) MR imaging focusing on affective modulation. The presented results highlight underlying brain mechanisms mediating exercise-mood relationships in healthy young adults.

COGNITIVE SESSION 2

Emotional processing in modern neuroscience – from human-rat dyads to VR devices

NEURAL CORRELATES OF EMOTION REGULATION DYSFUNCTION IN PROCRASTINATION

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Procrastination, the voluntary delay of beginning or completing an intended task despite the negative consequences of doing so, is a prevalent problem that entails severe academic, professional, financial, and health consequences. According to the influential emotion regulation perspective, procrastination occurs when people prioritize short-term mood repair over pursuing their long-term goals. This suggests that chronic procrastination may be related to emotion regulation dysfunction; however, more research is necessary, as no studies to date have directly investigated the behavioral and neurophysiological mechanisms that occur during the use of different emotion regulation strategies in high *versus* low procrastinating participants.

In the present EEG study, 80 participants were recruited based on their high or low scores in the Pure Procrastination Scale. With the use of emotion regulation task, we compared amplitudes of the late positive potential as indices of effectiveness of two emotion regulation strategies: cognitive distraction and cognitive reappraisal. We also assessed participants' preference for using either strategy. The results from high (*versus* low) procrastination individuals suggest a decreased ability to distract attention from negative

stimuli in this group. The results suggest that task delay in procrastination may be related to difficulty in detaching from the perceived aversiveness of the task.

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WOULD YOU LIKE TO MEET ME AT A PICNIC? A NEW METHOD FOR MEASURING SOCIABILITY BY AN FMRI PROCEDURE

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We present a new method to measure "sociability". It can be understood as a trait or state - tendency to interact with other people or to withdraw and self-isolate. We assume that the way of perceiving people's faces as more or less amiable, as well as willingness to know them better, could be an appropriate measure of this trait (or state). Apart from temperamental characteristics, some particular circumstances in day-to-day functioning, like sleep deprivation, can modulate conviviality and thus affect the quality of social relations in private and professional life.

PICNIC consists of 40 pictures of men and women from which participants choose those people they would like to know better – all during an MRI registration.

In this preliminary study data gathered from 10 subjects (9 females; mean age 22.3 ± 1.2 years) was analyzed. We applied ROI and IC analyses to examine the contrast between chosen and rejected stimuli. Important activations in visual and dorsal attention networks were observed. The most promising results are the visible contrasts in DMN and structures associated with brain reward network: anterior insula and caudate nucleus.

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MODELLING (AFFECTIVE) BEHAVIORS IN VIRTUAL ENVIRONMENTS

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One of the basic assumptions in affective computing is that there are physiological, quantitative correlates of emotional responses. However, the specificity of these reactions for individual emotions, as well as the cognitive aspect – how the excitation is interpreted by the feeling individual – remains problematic.

In the presented research, the subject of our interest was the possibility of modelling the behavior of VR simulation participants (Study 1, n=20) and users of a specially selected computer game (Study 2, n=18) based on information from ECG, GSR, eye tracker and other sensors.

The obtained results indicate that the interpretation of the stimulation of the sympathetic/parasympathetic nervous system can be significantly facilitated by strict control of the environment and tagging of the context enabled by the virtual nature of the settings.

The results of the research indicate that the virtual environment enables both the control of the subject's arousal and the interpretation of his psychophysiological states. Thanks to detailed data on the actions undertaken by the user, it is possible to create detailed models for further analysis.

It could be imagined that the virtual experimental environments may soon become one of the important tools in behavioral research regarding both human and non-human animals.

FEAR CONTAGION IN HUMAN-HUMAN AND HUMAN-RAT DYADS INVOLVES THE BASOLATERAL AND CENTROMEDIAL AMYGDALA

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Fear contagion is an automatic, unconscious process of aligning emotional distress of one animal to that of the other. Considering its important evolutionary role, we hypothesized it to be a cross-species phenomenon that would involve the amygdala. We thus investigated the social transfer of fear between humans and rats. The habituated rats were handled by familiar humans who underwent the fear conditioning task and following the interaction, the rats' amygdalae activations were analyzed using the c-Fos expression. Additionally, we used functional magnetic resonance imaging to investigate the activations in the amygdalar nuclei during fear contagion between human subjects. The rat amygdala was activated to a higher extent in experimental compared to control rats.

A significant change in activation was observed in both basolateral and centromedial nuclei, as compared to the average activations from the control group. The amygdala activation was also present in human data, and was also significantly increased in both basolateral and centromedial nuclei when compared to the baseline hemodynamic response. These results are the first to demonstrate that the same amygdalar subparts are activated in both human-human and human-rat fear contagion. This suggests that the common system of emotional communication may exist in both humans and rats.

Funding: Data collection and analysis were sponsored by National Science Centre grant 2015/19/B/HS6/02209. Ewelina Knapska was supported by European Research Council Starting Grant (H 415148).

AN ERP STUDY: CAN INTRA-UTERINE DEVICE USE ALTER EMOTION PROCESSING?

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Emotion processing depends on menstrual cycle, oral contraception use. Little is known whether the use of the hormonal intra-uterine device (IUD) affects emotional functioning. The aim of our study was to investigate IUD impact on women brain activity and perceived negativity.

Thirty-three IUD users, 33 women in follicular (NCF) and 28 women in luteal (NCL) phase of their menstrual cycle participated in the study. Participants were instructed to watch upcoming neutral, low and high negativity images and to evaluate perceived negativity after each stimuli while their electroencephalogram was recorded. Emotion perception related ERPs were evaluated. Emotional arousal and fatigue levels were measured using VAS scales.

There were no group differences in perceived negativity. Higher arousal level was positively related with negativity values while watching low and high negativity pictures. High and low intensity negative pictures induced higher LPP than neutral images (300 – 600 ms). Amplitudes of the early ERP components (P2, P3, N2) were lower for IUD users than for NCF and NCL women while watching negative stimuli (low + high negativity).

Results suggest possible emotion processing and attention alteration *via* changed brain activity when IUD is used.

The study was part of the project of the Baltic-German University Liaison Office supported by the German Academic Exchange Service (DAAD) with funds from the Foreign Office of the Federal Republic Germany.

COGNITIVE SESSION 3

Approaches to increase replicability in neuroscience – lessons learned from consortia, many analysts and cooperative data collection

Symposium organizer: Katharina Paul
(*University Hamburg, Germany*)

INCREASING RELIABILITY IN CLINICAL NEUROIMAGING: MEGA-ANALYTIC FINDINGS FROM THE ENIGMA TRANSGENDER PERSONS WORKING GROUP

Sven Mueller

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One common problem with clinical MRI research is that sample sizes of tested populations are small. This can be due to either a small prevalence rate or a difficulty to recruit a particular population. Individual neuroimaging studies of transgender persons have rarely achieved samples sizes of larger than 30 individuals (per group). To increase reliability of findings, the ENIGMA Transgender Persons Working Group, a consortium of presently 10 different labs around the world, was created. Here, the analysis of 800 structural brain scans of roughly 200 transgender men, 200 transgender women, 200 cisgender men and 200 cisgender women will be presented. Finally, in the last third of the talk I will touch briefly on a second way to increase reliability in neuroimaging, namely by rescanning the same participants within a session. Data from such a study also in transgender persons will be presented.

A NOVEL ATTEMPT TO IMPROVE REPLICABILITY OF EEG-PERSONALITY ASSOCIATIONS: THE COSCIENCE PROJECT

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The issues at the centre of the replicability crisis, such as low statistical power and undisclosed flexibility in data analysis, are amplified in research aiming to link individual differences in EEG markers to variations in personality due to between-subjects research designs and high complexity of data processing. The CoScience

Team, a collaboration of ten EEG-personality laboratories, employs the principles of cooperative forking paths analysis for the first time, aiming to address this unsatisfactory state of affairs by significantly increasing statistical power through sharing the load of data collection, and by eliminating undisclosed flexibility in data analysis. The latter is achieved through collaborative identification of both the most appropriate and all defensible pre-processing and analysis paths, and documentation of the resulting multiverse of millions of alternative analyses and results. These principles will be illustrated by data on the relationship between resting frontal alpha asymmetry and trait approach motivation.

EEG MANYPIPELINES: ONE DATASET MANY PIPELINES – HOW ROBUST ARE EEG FINDINGS?

Elena Cesnaite

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Analysis of electrophysiological data is marked by a large variability in the analytic approaches used to answer seemingly similar research questions. This type of variability might contribute to difficulty replicating and reproducing neuroscientific findings. Although few recent studies addressed the question on the impact of the analytic decisions to the result, it hasn't been thoroughly studied in a more naturalistic large-scale setting. EEG-ManyPipelines project aims to investigate robustness of electrophysiological findings across different analysis approaches provided by experienced EEG researchers analyzing a single dataset to answer 8 hypotheses. More than 300 teams consisting of 665 researchers applied for the project: Teams were encouraged to analyze the data and answer hypotheses with a pipeline and analysis methods of their choice. Importantly, teams were asked to use approaches that they would deem appropriate given their usual research practices. Within this symposium we would like to present the initial findings of the project.

ARTEM-IS: IMPROVING REPRODUCIBILITY AND REPLICABILITY OF EEG RESEARCH BY ENHANCING TRANSPARENCY

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The challenges of reproducibility and replicability have recently come into the spotlight, particularly since Open Science Collaboration published a paper evaluating state of the art in the field (Open Science Collaboration, 2015). Within the field of EEG, rich datasets and complex processing and analysis pipelines intensify this issue further. This problem has been recognized by multiple recent projects in the field EEGManyLabs, EEGManyPipelines, COBIDAS, and ARTEM-IS, which will be presented in this talk.

One of the challenges on the road to reproducible and replicable science is transparency in the scientific record. INCF Working Group on ARTEM-IS (Agreed Reporting Template for EEG Methodology – International Standard) aims to develop reporting tools for documenting methodological decisions of EEG studies and pipelines, as well as to engage the scientific community in developing and using such tools.

COGNITIVE SESSION 4

Plastic brain and language – adaptive changes of neural networks

RESTING-STATE FUNCTIONAL CONNECTIVITY BETWEEN CANONICAL RESTING-STATE NETWORKS CHANGES ACROSS A 7-MONTH TACTILE BRAILLE READING COURSE

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The human brain is active during rest and is organised into intrinsic functional networks. However, it remains unknown to what extent the communication within and between these functional networks changes in adults undergoing cross-modal training. Eighteen Braille-naive sighted participants took part in an extensive 7-month-long tactile Braille reading course. Seventeen age and gender-matched participants were also recruited as a passive control group. We measured functional connectivity within and between eight brain networks in a longitudinal resting-state fMRI study with five imaging sessions over seven months. We tested for a group-by-time interaction to determine whether training to read in a tactile domain produces changes in resting-state functional connectivity. While functional connectivity within resting-state networks did not change significantly,

we observed some changes in functional connectivity between resting-state networks. Specifically, functional connectivity between the Dorsal Attention Network (DAN) and Somatosensory Network (SMN) was strengthened during training in the Braille group with no changes in the Control group. This suggests that cross-modal training, such as learning to read in a different modality, might invoke changes in communication between separate brain networks. The increased functional connectivity between DAN and SMN might reflect increased attention paid to tactile signals in Braille learners.

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DISCOVERING PATTERNS OF ORTHOGRAPHIC AND PHONOLOGICAL PROCESSING IN CHILDREN WITH DEVELOPMENTAL DYSLEXIA – AN FMRI STUDY

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Fluent reading requires building orthographic and phonological representations (i.e., knowledge how to spell and pronounce words). In developmental dyslexia deficits in both areas are often reported. Thus, to specify those issues on a neural level, we designed an fMRI study in the Rapid Adaptation Paradigm in which we tested two groups of children (aged 9-13): control (CON; n=30) and with dyslexia (DYS; n=33). In scanner we repeatedly presented words that shared phonology but differ in orthography (homophones, e.g., kret-kred), shared both (kret-kret) or differed in both (kret-noga). Our results on a whole-brain level confirmed between-group differences in the reading network; e.g., in homophone condition in the left IFG (opercularis, triangularis) (CON>DYS, .001, p<0.05, FWEcc) – regions involved in phonological processing also often disrupted in dyslexia. During presentation we will introduce ROI comparisons based on an independent localizer task that allows to define individual orthographic and phonological areas for each participant. We aim to demonstrate the atypical rapid adaptation patterns in DYS. Finally, we will employ multivariate pattern analysis to discuss the stability of representations. DYS should produce less stable neural representations indicating general problems with processing lexical stimuli.

Funding: "Neural and cognitive basis of spelling impairment" National Science Centre grant 2019/35/HS6/01677.

BRAIN BASIS OF SPEECH PRODUCTION IN THE NATIVE AND A SECOND LANGUAGE: AN FMRI STUDY USING FUNCTIONAL LOCALIZERS

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This study attempted to characterize neural basis of speech production in the native (L1) and a second (L2) language. Many neuroimaging studies found differences in brain activity corresponding to speaking in a second language compared to the native language (L2 *vs.* L1). However, it is unclear whether these differences reflect increased engagement of cognitive control or differences in language-specific computations. We addressed this question in an fMRI study in which forty-one Polish-English bilinguals named pictures. We compared activity within the domain-general cognitive control network and the language network (bilateral ROIs) to examine which is more sensitive to L2 processing (i.e., L2>L1). We also looked at three more specific functional networks supporting articulation, interference resolution and lexical retrieval. Our results show that speaking in L2 compared to L1 engaged more strongly the left but not right domain-general cognitive control network. On the contrary, we found no differences between languages in the left language-specific network while the right language-specific network was engaged more strongly in processing of L1 compared to L2. Production in L2 was also associated with a higher activity within left-lateralized ROIs in networks engaged in interference resolution and lexical retrieval but not in articulation.

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LONG- AND SHORT-TERM ADAPTATION OF THE BILINGUAL LANGUAGE SYSTEM TO DIFFERENT LANGUAGE ENVIRONMENTS: ELECTROPHYSIOLOGICAL EVIDENCE

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The present study explored how the neural mechanisms of native language lexical access in migrants change after long-term immersion in a foreign language (L2) environment and after reimmersion in a native language (L1) environment. We tested Polish-English migrants living for about ten years in the UK (L2 environment) and Polish-English controls living in Poland (L1 environment). All participants performed a picture-naming task while we recorded their electrophysiological responses. The migrants were tested before and after visiting the L1 environment, while the controls were tested twice in their L1 environment. We focused on exploring two event-related components associated with the ease of lexical access: P2 and N300. We found that re-immersion in L1 modulated the P2 in the migrants, such that higher amplitudes were evoked in response to picture naming during immersion in the L2 environment compared to after a reimmersion in the L1 environment. However, we did not find a modulation of the N300 by group or by reimmersion. These results seem to indicate that migrants experience increased difficulty in the L1 lexical access while being immersed in an L2 environment, which can be overcome after a short-term reimmersion in the L1 environment.

Funding: The research was possible thanks to a National Science Centre grant (2015/18/E/HS6/00428) awarded to Z.W.

INVESTIGATION OF EEG SPECTRAL AND TEMPORAL PROPERTIES WITHIN THE CONCURRENT HIERARCHICAL TRACKING (CHT) PARADIGM

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Concurrent Hierarchical Tracking (CHT) is a paradigm allowing for observation of neural activity associated with rhythmicity of auditory stream stimuli composed of words, phrases or sentences. Within this paradigm, durations of each stimulus entity (e.g., monosyllabic words), constructed phrases and sentences are constant. Therefore, the stimuli streams contain predetermined frequencies, which are related to the rhythmicity of words, phrases or sentences. Comprehension of single words may lead to the emergence of higher linguistic entities, such as phrases or sentences (e.g., small dog eats bone). Standard approach to detection of these frequencies in EEG was based upon Inter-Trial Phase Coherence. However, this approach detects only phasic relationships between trials, without inspection of their spectro-temporal properties.

We present preliminary results of ERP and spectro-temporal analyses conducted on the basis of the pilot EEG datasets (N=9) recorded in the CHT paradigm, revealing statistically significant effects in the time-frequency space and ERP. Obtained results may help us to better understand the dynamics of activities related to hierarchical language comprehension.

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COGNITIVE SESSION 5

Neuroimaging of the reading brain

Symposium organizer: Katarzyna Chyl
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CAPTURING LETTER AND SOUND LEARNING IN TYPICAL AND DYSLEXIC READERS

Milene Bonte

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The formation of efficient associations between visual and spoken language representations forms a fundamental step in reading development. Although we have a fairly good understanding of how our brain processes already learnt associations, we know very little about underlying learning processes. In this talk I will discuss how behavioral, EEG and fMRI measures can be used to track neurobehavioral changes during letter and speech sound learning, and how these changes may relate to dyslexia.

EARLY READING SKILLS AND THE VENTRAL OCCIPITO-TEMPORAL CORTEX ORGANIZATION

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Learning to read impacts the way the ventral occipitotemporal cortex (VOT) reorganizes. The postulated underlying mechanism of neuronal recycling was recently revisited. An experimental data showed that voxels weakly specialized for visual processing keep their initial category selectivity, while acquiring an additional, stronger

responsivity to written words. Here, we examined a large and diverse group of six-year-olds prior to literacy training (N=72) using various data analysis techniques (univariate, multivariate, rapid adaptation) and types of stimuli (print, symbols, houses, faces) to further explore how VOT changes and adapts to reading. We found that only print activated a wide network of language related areas outside of the bilateral VOT, and the level of reading skill was related to the extent and strength of this activation. Adaptation effect was not directly related to the level of reading skill, but revealed the emergence of the reading network in readers. Importantly, we found that the reorganization of the VOT is not an "invasion" by reading acquisition – voxels previously activated for faces started to respond more for print, while at the same time keeping their previous function. We can thus conclude that the revised hypothesis of neuronal recycling is supported by our data.

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THE DEVELOPMENT OF THE ORTHOGRAPHY-PHONOLOGY INTEGRATION IN OCCIPITOTEMPORAL CORTEX AND ITS RELATIONS TO THE READING ACQUISITION

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The region of the left ventral occipitotemporal cortex (VOTc) encompassing Visual Word Form Area is considered to host orthographic representations of words. Even though this area was studied in visual word processing, there is evidence of multimodal engagement of the left VOTc in spoken language. It is supposed to facilitate the integration of phonological and orthographical representations needed for an effective reading acquisition. To investigate the development of the left posterior and anterior VOTc involvement in spoken language processing and its relations to the reading ability we tested 47 Polish beginning readers at the beginning of the formal literacy acquisition and two years later. In fMRI tasks children had to decide whether two auditory words start with the same sound (phoneme matching), if they rhyme (rhyming) or if they are identical (word matching). Univariate and multivariate approaches showed the increase of integration proccess with the time of schooling. The most relevant integration processes occurs on a smallest grain size of phonological processing in agreement with the high transparency of Polish orthography and differently than in opaque English orthography.

Funding: This research has been made possible by the Kosciuszko Foundation scholarship at Vanderbilt University, Nashville, TN.

INVESTIGATING NEURAL NOISE IN DYSLEXIA USING FUNCTIONAL MAGNETIC RESONANCE SPECTROSCOPY (FMRS) AND EEG POWER SPECTRUM

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Dyslexia is a developmental disorder characterized by a specific difficulty in learning to read and write that cannot be explained by low intellectual level or by incorrect teaching methods in school. According to the neural noise hypothesis, dyslexia is a consequence of disturbance in synaptic transmission. In particular, an imbalance between main excitatory (glutamate) and main inhibitory neurotransmitter (GABA) is assumed – specifically with elevated glutamate concentrations in dyslexia. However, experimental data verifying this hypothesis is still missing. During our talk, we will present results from our study in which we tested the neural noise hypothesis in dyslexia in adolescents and young adults (aged 15-24) using two methods. First, a direct measure of neurotransmitters' concentrations in the course of reading words (i.e., functional magnetic resonance spectroscopy, fMRS) and second, an indirect indicator of excitatory to inhibitory neurotransmitters' ratio (i.e., 1/f signal from EEG power spectrum).

Funding: This study was funded by the Polish National Science Center OPUS grant (2019/35/B/HS6/01763) awarded to Katarzyna Jednoróg.

COGNITIVE SESSION 6

Search for neural biomarkers of aware consciousness

THE NEXT TRIAL WILL BE CONFLICTING! NEURAL UNDERPINNINGS OF PROACTIVE ACTION CONTROL

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The talk will investigate the neural basis of proactive adjustments of executive control, and their modulatory effects on online processing of response conflict. In two EEG experiments, participants performed the flanker task in which conflict trials were signaled by predictive (red) cue. We observed improved behavioral performance in the predictive condition, suggesting that participants proactively used the cues to prepare for the upcoming demands. Conflict-related modulations of midfrontal EEG component N2, theta power, and theta phase synchrony were smaller in the predictive than in the neutral condition. This suggests that proactive control suppressed the impact of incongruent flankers in conflict trials, so that the conflict was reduced, and so was the online control involvement. Conflict-cueing also increased midfrontal theta power and connectivity between occipital and midfrontal sites before target onset, suggesting pre-activation of the control processes beforehand. Unlike the online control, the proactive control triggered a burst of theta power in the right hemisphere's dorsal and ventral lateral prefrontal cortices. In other words, two separate components of frontal theta power were observed during the proactive adjustments of control. This indicates that the two modes of control involve partially unique neural processes.

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PERCEPTUAL AWARENESS NEGATIVITY – DOES IT REFLECT AWARENESS OR ATTENTION?

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A growing body of evidence indicates that Perceptual Awareness Negativity (PAN) – a negative ERP component observed at posterior brain regions around 200 ms after the stimulus presentation – is a robust correlate of phenomenal awareness. However, in terms of spatio-temporal features PAN is very similar to the previously described ERP correlates of selective attention (e.g., SN and N2pc). Therefore, whether PAN is indeed a specific mechanism of perceptual consciousness or rather an index of attentional amplification remains to be addressed. To this end we designed two experiments in which stimulus awareness and various aspects of visual attention were manipulated orthogonally. Participants were presented with letters, which were either backward-masked or unmasked. Letters were presented on the attended or unattended side of the screen and were defined as targets or task-irrelevant distractors. Our analysis revealed that PAN's amplitude was more negative in response to letters presented on the attended side of the screen (in comparison to letters on the unattended side) or defined as targets (in comparison to distractors). Therefore our study suggests that PAN is modulated by both spatial attention and task-relevance and thus should not be considered a "pure" and specific correlate of consciousness.

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TOWARDS UNDERSTANDING THE ROLES OF THE RTPJ AND THE MPFC IN THEORY OF MIND: FMRI STUDY

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In the current study we aimed to inform the ongoing debate concerning the neurocognitive basis of the Theory of Mind (ToM) as a crucial but complex social-cognitive ability. by investigating the functional divisions within the dedicated ToM network.

To this end 61 healthy adults took part in an fMRI study in which we examined the responses of the key nodes of the ToM network taking into consideration the phase of others' mental state processing. We explored the activity patterns during two ToM tasks engaging belief-reasoning. We expected to observe differential patterns of activity related to the phases of 1) formation of mental state representation and 2) reporting others' beliefs.

We demonstrate a division of function between the right posterior temporo-parietal junction (RTPJp) and the medial prefrontal cortex (mPFC) during ToM task performance. The former seems crucial for representing the mental states whereas the latter is rather engaged in reporting them. Moreover the activity of mPFC seems not to be specific for ToM. This is further supported by the seed-to-ROI resting-state fMRI analysis. Our results add to the evidence that the "core" of the ToM network is functionally heterogeneous and probably hierarchically organized.

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CHIRP-EVOKED AUDITORY STEADY-STATE POTENTIALS IN GAMMA BAND AS A DIAGNOSTIC BIOMARKER IN DISORDERS OF CONSCIOUSNESS

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Diagnosis of the level of awareness in disorders of consciousness after severe brain injury is a challenging issue. In order to establish an EEG-based biomarker of awareness we have tested auditory steady-state responses (ASSRs) in a group of 58 DOC patients (diagnosed as conscious and unconscious) and 20 healthy control participants. Condition of DOC patients were assessed with the use of Coma Recovery-Scale Revised (CRS-R) tool. To evoke ASSRs, we used chirp-modulated acoustic periodic stimulation in two variants: narrow-band chirps (NBC, 1000 Hz tones, modulated within the range of 25-55 Hz) and wide-band chirps (WBC, white noise bursts chirp-modulated within 30-100 Hz range). Both types of stimulation were decreasing in frequency during presentation. The inter-trial phase clustering parameter was used to evaluate the strength of the response. Responses to NBC stimulation allowed for discrimination between unconscious and conscious conditions of DOC. The responses to WBC were significantly weaker in the DOC patients group than in the control group, yet we did not found significant differences between unconscious and conscious DOC group. The results show the promising perspective of using gamma-band auditory responses as a potential biomarker of consciousness in the studied patient group.

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INDIVIDUAL DIFFERENCES IN TEMPORAL INFORMATION PROCESSING ARE REFLECTED IN EEG ACTIVITY

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As time is omnipresent in our life, the efficient Temporal Information Processing (TIP) is crucial not only for our every-day activity, but also for mental processes underlying human cognition, like language, perception, memory, motor control, etc. This study was aimed at testing relationships between individual differences in TIP and EEG activity of the brain.

Eighty-three healthy participants (Mage=25 years) completed: (1) Temporal-Order Judgement task (TOJ) which measured the efficiency of TIP on the millisecond level, and (2) EEG resting state procedure. On the basis of these TOJ values achieved in TIP task, subjects were classified into two groups characterized by high (HTE) or low (LTE) temporal efficiency. The analyses of theta, alpha, beta and gamma power activity in HTE and LTE groups were performed using U Mann-Whitney rang test. We indicated that HTE showed significantly lower average range of frontal gamma than LTE ($U=374$; $p<0.05$).

These results showed that more efficient millisecond TIP was associated with less gamma power. It is consistent with the hypothesis that better cognitive performance may be linked to the lower cortical energy consumption. Our study suggests that temporal resolution is related to the dynamics of EEG activity in normal young adults.

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COGNITIVE SESSION 7

Pupillometry: Getting information in the glimpse of an eye

Symposium organizer: Beaupoil Laurent
(*Institute of Psychology, Jagiellonian University, Krakow, Poland*)

PUPIL DILATATION INDEXES INFORMATION GAIN

Alexandre Zénon

Université de Bordeaux, France

Under constant lighting conditions, the diameter of the eye pupil, thought to index brain arousal, varies in response to many cognitive variables, such as attention, task difficulty, surprise, urgency, etc. In this presentation, I will show that these cognition-induced pupillary dilations have a quantitative relationship with information gain, an information-theoretic measure of task complexity that corresponds to the magnitude of the update between prior and posterior beliefs. I will introduce the theoretical concepts and will present some of the experimental evidence supporting this hypothesis. I will then discuss how it has the potential to explain the ensemble of relationships shown so far between cognition and pupillary dilation.

DEVELOPING RELIABLE INTER-INDIVIDUAL CHARACTERIZATION THROUGH PUPILLOMETRY: A FIRST APPROACH USING VARIATIONAL AUTO ENCODERS

Laurent Beaupoil

Institute of Psychology, Jagiellonian University, Krakow, Poland

Pupil size variations are now widely recognised to be linked to a wealth of cognitive functions. We reasoned that this relationship between pupillometry and cognition may provide us with a way to probe psychological inter-individual differences non-invasively and reliably. During this presentation, I will show you the results of the first of four planned approaches of interindividual clusterisation based on pupil response by means on Variational Auto-Encoders. Although the results of this first naive approach were not sufficient to provide reliable separation of individuals, they showed encouraging trends and helped us prepare the next steps.

ANALYSIS OF PUPIL SIZE DYNAMICS DURING PRE-TASK BASELINE AND ITS RELATION TO STRATEGY PREFERENCE IN MULTI-ATTRIBUTE CHOICE

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Complex decision making requires cognitive effort, and attentional processes underlying effort can be indexed by changes in pupil size. Pupil dynamics has been linked to cognitive task demands, however baseline pupil size has also been linked to individual differences in information processing capacity. In the present study, we examined tonic changes of pupil size during two-minute baseline period in relation to the preference for simple *vs.* complex strategies in multi-attribute choice. Participants performed a choice task where they chose one of two diamonds based on six cues, and their preference for either a complex Weighted Additive (WADD) strategy or a simple heuristic Take The Best were calculated. Pupil size changes were recorded for 2 min before the task performance. Based on previous research, we analysed the baseline pupil signal to identify its various frequency components, in order to explore their relation with strategy preference, and we found only limited evidence for this relation. In contrast, we found substantial evidence for the relation between strategy preference and the baseline pupil signal averaged across four blocks 30 s each. We discuss this evidence in relation to theories and findings on arousal and effort in complex cognitive tasks.

EMOTION SCHEMA EFFECTS ON ASSOCIATIVE MEMORY DIFFER FOR DISGUST AND FEAR

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Previous behavioral and neuroimaging studies have consistently reported that memory is enhanced for associations congruent or incongruent with the structure of prior knowledge, termed as schemas. However, it remains unclear if similar effects arise with emotion-related associations, and whether they depend on the type of emotions. Here, we addressed this question using a novel face-word pair association paradigm combined with fMRI and eye-tracking techniques. In two independent studies, we demonstrated and replicated that both congruency with emotion schemas and emotion category interact to affect associative memory. Disgust was remembered better than fear, and only disgust activated left IFG stronger during encoding of congruent *vs.* incongruent pairs, suggestive of deeper semantic processing for the associations. In addition, successful memory formation for congruent disgust pairs was associated with a higher pupil dilation index related to sympathetic activation, longer gaze time on words compared to faces, and more gaze switches between paired words and faces. This was reversed for fear-related congruent pairs where the faces attracted longer gaze time (compared to words). Overall, our results provide converging evidence that congruency with available emotion schemas influence memory associations in a similar manner to semantic schemas. However, these effects vary across distinct emotion categories.

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BASELINE PUPIL SIZE PREDICTS STRATEGY USE IN COMPLEX DECISION MAKING

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Pupil size provides insights into cognitive processes, e.g., task-related pupil dilation is an accurate measure of cognitive effort and control in various tasks. In our study we went beyond these findings to explore whether baseline pupil size can predict subsequent strategy use in complex decision-making. Complex decision strategies involve intensive cognitive effort and control, thus they pose capacity demand on the decision maker. If pupil size is related to cognitive load, then baseline pupil size should predict subsequent strategy use. To verify this hypothesis, we conducted a process tracing decision making study, in which participants decided which of two diamonds is more expensive, based on six different cues. We measured how much information participants acquired before the choice and we identified the strategy the participants used, based on their choices. Using correlation and linear model analysis, we found that large pre-task baseline pupil size is associated with using simple choice strategy, yet this relationship is moderated by task conditions and individual responsiveness to the task. These results show that, with some limitations, we can predict subsequent decision making strategy from a relatively simple measurement of baseline pupil size.

COGNITIVE SESSION 8

Specificity of language network in the contingentally blind brain

MIRROR INVARIANCE FOR OBJECTS AND BRAILLE LETTERS IN CONGENITALLY BLIND PEOPLE – A BEHAVIORAL AND FMRI STUDY

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Mirror-images of objects are recognized as the same object, but letters aren't ("d" is not "b"). Studies show that the fusiform cortex is important in mirror discrimination in sighted for words and letters. Moreover, the congenitally blind could break mirror invariance for Braille letters like the sighted. Here, we investigated which neural mechanisms underlie this process.

Nineteen congenitally blind adults participated in our experiments. First, they performed two behavioral same-different tactile comparison tasks. Stimuli were pairs of Braille letters, geometric shapes, and everyday objects (e.g., toothbrush) in same ("p" and "p"), mirror orientation ("p" and "q"), and different ("p" and "z") pairs. In the fMRI part, Braille letters and everyday objects in the above-mentioned formats were presented in a priming paradigm.

Behavior showed that subjects had shorter response times and higher accuracy for Braille letters and objects than for shapes. fMRI results showed mirror priming for objects in the fusiform cortex. In addition, an early visual cortex area distinguished between the left-right orientation of Braille letters.

Our results demonstrate that the fusiform cortex of the blind exhibits mirror invariance for objects similar to the one observed in the sighted. Mirror invariance for letters, however, occurs in the reorganized visual cortex.

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PLASTICITY OF GRAMMATICAL AND SEMANTIC PROCESSING NETWORKS IN BRAINS OF CONGENITALLY BLIND INDIVIDUALS

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Language processing involves similar brain regions across languages and cultures. This observation might suggest that specific brain regions are hard-wired for language, and that language network can develop only in these regions. However, this view has been challenged by certain embodied cognition and neuroplasticity theories, which predict that different sensorimotor experience can lead to qualitatively different implementations of language in the brain. Here, we tested this prediction by studying language processing in sighted and congenitally blind individuals, that is, in two groups with systematically different sensorimotor experience. We enrolled 20 blind and 20 sighted participants in an fMRI experiment, in which they performed linguistic transformations of concrete nouns and verbs, abstract nouns and verbs, and pseudo nouns and verbs. We used multi-voxel pattern analysis (MVPA) to reveal brain networks representing grammatical (nouns, verbs) and semantic (abstract, concrete, pseudo) characteristics of words. We observed between-group differences primarily in left frontal and temporal regions, known to be implicated in grammatical and semantic processing in sighted individuals. Thus, our findings suggest that differences in sensorimotor experience modify salience of specific linguistic representations in canonical language regions. However, an overall shape of the language network seems relatively robust to changes in sensorimotor experience.

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THE PERCEPTION OF INTEROCEPTIVE SIGNALS IN BLIND INDIVIDUALS

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Visual deprivation is associated with massive cross-modal plasticity. Here, we examined the influence of blindness on two sensory submodalities of interoception: cardiac interoception and affective touch. We tested 36 blind individuals and 36 age and sex-matched sighted volunteers. In experiment 1, we assessed their cardiac interoceptive abilities using the heartbeat counting task. In experiment 2, we measured perception of skin-mediated interoceptive signals by asking about the pleasantness of touch delivered in a C-tactile (CT) optimal *versus* a CT non-optimal manner, and also implemented a control task of discriminative touch abilities, the grating orientation task. We found that blind individuals perform significantly better than sighted in the task measuring their cardiac interoceptive accuracy. In the case of affective touch, we found that blind individuals rate the touch as significantly more pleasant on the palm as compared with the forearm. We also replicated the previous findings showing enhanced discriminative tactile acuity in the blind. We conclude that visual deprivation leads to enhanced interoception, which has important implications for the study of the extent of massive cross-modal plasticity after visual loss.

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DECODING SPOKEN WORDS IN BRAINS OF SIGHTED AND CONGENITALLY BLIND INDIVIDUALS

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Spoken word comprehension involves a wide network of frontal, parietal and temporal brain regions, primarily in the left hemisphere. Intriguingly, in blind individuals, listening to spoken words also activates the visual cortex. Here, we used fMRI and mutli-voxel pattern analysis (MVPA) to address two questions: (1) Does visual cortex activation in blind individuals represents differences between specific spoken words? (2) Can spoken word representation be observed also in the visual cortex of sighted individuals? We studied 20 sighted and 17 congenitally blind participants listening to spoken words and making semantic decisions on word referents. We found that words can be decoded from primary visual cortex activation in both blind and sighted participants. Furthermore, searchlight analysis showed that brain networks representing differences between spoken words are overall very similar in both participant groups. We conclude that the overall shape of the spoken word comprehension network, as investigated with MVPA, is robust to changes in visual experience. We also suggest that visual cortex responses to spoken words, observed in blind individuals, might reflect an increase in visual cortex sensitivity to information that is typically represented in this region.

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FUNCTIONAL INVOLVEMENT OF OCCIPITAL CORTEX DURING READING AND SPEECH PROCESSING IN CONGENITAL BLINDNESS: EVIDENCE FROM FMRI AND TMS

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Multiple studies have shown that the visual cortex of blind subjects responds to tactile or auditory stimuli in a functionally specific fashion. However, the degree of retained cortical functionality is still debated. Here, we are investigating the roles of the "visual" cortex of early blind and sighted people in reading and speech processing. Using fMRI we identified neuronal responses to words, pseudowords, and

low-level sensory stimuli during reading and speech 1-back tasks. While the blind early visual cortex (EVC) responded to linguistic and simple sensory stimuli, activity in the left ventral occipitotemporal cortex (vOTC) was specific to language. Crucially, these patterns occurred both for tactile and auditory processing. Similar, reading-specific patterns were observed in sighted subjects, with no responses to auditory stimuli. Currently, we are using transcranial magnetic stimulation (TMS) to trace the information flow between low-level and higher-order visual areas. With 20Hz paired-pulse TMS, we are disrupting neuronal processing in the EVC and left vOTC during reading and speech processing. Therefore, this project investigates the sensory-specific hierarchy of information processing in the blind visual cortex. The results should contribute to a deeper understanding of the nature of the blind visual cortex in the context of currently discussed theoretical frameworks.

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MEDICAL SESSION 1

Biomarkers of Neurodegeneration

Symposium organizer: Przemysław Kac
(*University of Gothenburg, Sweden*)

CSF AND PLASMA BIOMARKERS FOR ALZHEIMER'S DISEASE – UPDATE ON PERFORMANCE AND APPLICATIONS IN THE CLINIC

Kaj Blennow
University of Gothenburg, Sweden

Cerebrospinal fluid (CSF) biomarkers reflecting the core AD pathologies amyloid deposition (A), tau pathology (T), neurodegeneration (N) have been developed and show very high performance for diagnosis. These tests are also available on fully automated lab analyzers, with superior precision. Newly developed blood biomarkers for AD show promise for use as screening tools and therapy monitoring, which will be of great importance when the new amyloid immunotherapies will be available in the clinic. The plasma Ab42/40 ratio, measured using either immunoassays or immunoprecipitation – mass spectrometry (IP-MS) methods show high concordance (AUCs of 80-90%) with brain amyloidosis evaluated by PET. However, the effect size (fold change) in PET positive cases for the Ab42/40 ratio is low, when measured in plasma, with only around 10% decrease and a major overlap.

Very promising data have been reported for several phosphorylated tau species (P-tau181, P-tau217, and P-tau231) in blood, showing a specific increase in AD and high concordance with tau PET. In addition, plasma P-tau is increased in cognitively unimpaired elderly who have positive amyloid, but negative tau, PET scans. Recent studies show high correlations between these P-tau species in both CSF and plasma, suggesting that differences are minor.

Neurofilament light (NFL) levels are increased in both CSF and blood in AD, but NFL is a general neurodegeneration biomarker showing high levels in many other neurodegenerative disorders. AD. High plasma GFAP is also found in cases with PET evidence of brain amyloidosis and shows promise as a biomarker for glial activation and neuroinflammation.

To implement the blood biomarkers in clinical routine diagnostics, data on the robustness of these biomarkers is needed. For a robust biomarker, the combined biological, pre-analytical, and analytical variability is markedly lower than the fold change (percent difference between patients and controls), also with repeated measurements. For this reason, blood biomarkers may better fit for risk prediction, in algorithms together with APOE and age, than as diagnostic tools. Even so, blood biomarkers will be very useful in the clinical setting.

BRAIN-DERIVED TAU: A NOVEL BLOOD-BASED BIOMARKER FOR ALZHEIMER'S DISEASE-TYPE NEURODEGENERATION

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Blood-based biomarkers for amyloid-beta and phosphorylated-tau (p-tau) show good diagnostic accuracies and agreements with their corresponding cerebrospinal fluid (CSF) and neuroimaging biomarkers in the amyloid/tau/neurodegeneration (AT(N)) framework for Alzheimer's disease (Alzheimer's disease). However, the blood-based neurodegeneration marker neurofilament light (NfL) is not specific to Alzheimer's disease while total-tau (t-tau) shows lack of correlation with CSF t-tau. Recent studies suggest that blood t-tau originates principally from peripheral, non-brain sources. We generated an anti-tau antibody that selectively binds brain-derived tau (BD-tau) and avoids the peripherally-expressed "big tau" isoform. We applied this antibody to develop an ultrasensitive blood-based assay for BD-tau, and validated it in five independent cohorts (n=609) including a blood-to-autopsy cohort, CSF biomarker-classified cohorts, and memory clinic cohorts. In paired samples, serum and CSF BD-tau were significantly correlated (r=0.85,P<0.0001), while serum and CSF t-tau were not (r=0.23,P=0.3364). Blood-based BD-tau showed equivalent diagnostic performance as CSF t-tau and CSF BD-tau to separate biomarker-positive Alzheimer's disease participants from biomarker-negative controls. Furthermore, plasma BD-tau accurately distinguished autopsy-confirmed Alzheimer's disease from other neurodegenerative diseases (AUCs=86.4%) while NfL did not (AUC=54.3%). These performances were independent of the presence of concomitant pathologies.

Plasma BD-tau (r=0.52-0.67 p=0.003), but not NfL (r=-0.14-0.17 p=0.501), was associated with global and regional amyloid-plaque and neurofibrillary-tangle counts. These results were further verified in two memory clinic cohorts where serum BD-tau was increased in Alzheimer's disease but not in a range of other neurodegenerative disorders, including frontotemporal lobar degeneration and atypical Parkinsonian disorders. Notably, plasma/serum BD-tau correlated with NfL only in AD but not in other neurodegenerative groups. Across cohorts, plasma/serum BD-tau was associated with CSF and plasma AT(N) biomarkers and cognitive function.

BD-tau is a new blood-based biomarker that outperforms plasma t-tau and, unlike NfL, shows specificity to Alzheimer's disease-type neurodegeneration. Thus, BD-tau demonstrates potential to complete the AT(N) scheme in blood, and will be useful to evaluate Alzheimer's disease-dependent neurodegenerative processes for clinical and research purposes.

P-TAU212 AS SUPERIOR BIOMARKER FOR ALZHEIMER'S DISEASE DIAGNOSIS

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Biofluid based phosphorylated-tau (p-tau) variants measurements are providing great diagnostic value in Alzheimer's disease (AD). Core cerebrospinal fluid (CSF) biomarkers are total-tau, p-tau181 and the amyloid ß42(Aß42) to amyloid ß40(Aß40) ratio (Aß42/40). However, tau phospohorylation at other epitopes may provide novel insights into AD pathogenesis. We aimed to investigate if p-tau212 has capacity to differentiate between biomarker-negative controls or biomarker-positive AD and to correlate with the core CSF biomarkers. We developed and validated a novel, ultrasensitive immunoassay for p-tau212. We then measured this biomarker in CSF of n=40 participants (n=20 biomarker-negative controls and n=20 biomarker-positive AD) and its diagnostic accuracy and correlations were evaluated.

CSF p-tau212 was increased in biomarker positive-AD *versus* biomarker-negative controls (median=213.1 pg/ml *versus* 30.07 pg/ml; P<0.0001), AUC=100% (95%-CI-100%). We observed positive correlation between CSF p-tau212 and each of CSF p-tau181 (r=0.91; P=<0.0001) and CSF total-tau (r=0.95; P=<0.0001). We observed negative correlation (r=-0.62; P=<0.0001) between CSF p-tau212 and CSF Aß42.

Our results show CSF p-tau212 can effectively discriminate biomarker-positive AD from biomarker-negative controls in this relatively small cohort. Further measurements will be done to compare utility of p-tau212 with other conventional p-tau epitopes such as p-tau217 and p-tau231. Efforts are underway to develop a blood-based version of the p-tau212 biomarker.

PRESUMED RESTING-STATE EEG BIOMARKERS OF ALZHEIMER'S DISEASE: AN EVIDENCE FROM HEALTHY RISK-CARRIERS

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Alzheimer's disease (AD) is a global problem, with a usually delayed diagnosis and no effective drugs. Earlier diagnosis and prevention of AD could be facilitated by biomarkers, which should be detectable with inexpensive and widely available techniques such as EEG (electroencephalography). A number of changes in spontaneous EEG have been shown in patients with AD and mild cognitive impairment.

We have tested 79 healthy middle-aged adults during a resting-state EEG session. AD risk genes, the APOE (rs429358/rs7412) and PICALM (rs3851179/rs541458) alleles were determined using the traditional Sanger sequencing protocol.

We have found several signal features in the AD risk-carriers group, including the so-called "slowing of the EEG" (which is the most noticeable and sensitive EEG marker among AD patients), i.e., higher delta relative power, lower alpha relative power, and slower alpha frequency (in males). A loss of signal complexity was also noticeable among the AD risk-carriers, in line with earlier reports that these two measures, complexity and EEG slowing, are strongly related.

These results are consistent with the current literature describing EEG features in AD patients, and were obtained for the very first time in healthy risk-carriers. However, longitudinal studies are planned to confirm them as valid AD biomarkers.

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MEDICAL SESSION 2

Translational Neuropsychiatry

EXPOSURES AND NEUROPSYCHIATRIC DISORDERS: SMALL RNAS AND THEIR BIG FAT PARTNERS

Ali Jawaid

BRAINCITY: Center of Excellence for Neural Plasticity and Brain Disorders, Poland

The life experiences and environmental conditions are strong determinants of brain health in humans. Long-term exposure to adverse conditions, such as traumatic experiences or nutritional insults can not only lead to brain diseases in the exposed individuals but such disease susceptibilities may also be transmitted to their offspring. Two important molecular pathways connect environmental exposures to brain disorders; epigenetic factors, such as non-coding RNAs (ncRNAs), and metabolic factors. Notably, our research shows a causal role for ncRNAs in intergenerational transmission of neuropsychiatric disease risk after early life trauma and a potential role for metabolic pathways in mediating this transmission.

CONSISTENT MIRNA SIGNATURES OF CHILDHOOD TRAUMA ACROSS DIFFERENT BODY FLUIDS IN HUMANS

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The main goal of this project is to systematically examine miRNA changes in human body fluids, that are relevant to long-term sequelae of childhood trauma including its intergenerational transmission. Small RNA sequencing followed by RT-qPCR assays were performed to identify and validate differentially regulated miRNAs in the serum of children with recent trauma in the form of paternal loss and maternal separation (PLMS), sperm of adult men with history of complex trauma, and milk from lactating mothers with history of childhood trauma. Pathway analysis for altered miRNAs was performed based on the TarBase database.

Small RNA sequencing analysis revealed 48 miRNAs to be differentially expressed in the serum of PLMS children *vs.* control; whereas 29 miRNAs were differentially expressed in the sperm of adult men with a history of trauma. Several differentially regulated miRNAs over-lapped between analyses. Furthermore, the pathway analysis and functional relevance of the altered miRNAs suggest potential implication of lipids-associated miRNA carriers in the observed changes.

This study found overlapping miRNA changes in a range of body fluids after childhood trauma that seem to be conserved across diverse cohorts and age-groups. The close relevance of these miRNAs to lipid-derived carriers is the premise of our current investigations.

SEVERITY OF DEPRESSIVE SYMPTOMS IS ASSOCIATED WITH AUTISTIC TRAITS AND MEDIATED BY MENTALIZATION, ADULT ATTACHMENT STYLE AND PSYCHOLOGICAL FLEXIBILITY

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Individuals with autism spectrum disorder (ASD) are four times more likely to experience depression in their lifetime than neurotypical individuals, according to a recent meta-analysis. However, the nature of this relationship remains unclear. We hypothesized that attachment style, mentalization, social support and psychological flexibility might affect depressive symptoms, but due to difficulties in theory of mind and social communication in ASD, the extent of their effects differs between individuals with and without an autism spectrum disorder diagnosis. 1783 participants (ASD N=133, non-ASD N=1650) completed an online questionnaire, comprising Autism Spectrum Quotient (AQ), Beck Depression Inventory (BDI), Mentalization Questionnaire (MZQ), Adult Attachment Scale (AAS, anxious and avoidant), Multidimensional Scale of Perceived Social Support (MSPSS) and Acceptance and Action Questionnaire-II (AAQ-II). We performed a moderated mediation analysis. The significant association between AQ and BDI was partially mediated by MZQ, AAS, MSPSS and AAQ, but ASD diagnosis moderates this effect. In the non-ASD group MZQ and AAQ-II, while in ASD group Avoidant Attachment and AAQ-II have significant indirect effects. In summary, in ASD avoidant attachment style, while in non-ASD mentalization has a larger indirect effect on depressive symptoms. This difference is of great importance for the design of therapeutic interventions.

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VALIDATION OF A NEW MOUSE MODEL FOR AUTISM SPECTRUM DISORDER RESEARCH

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Tcf7l2 is a high confidence risk gene for autism spectrum disorder, but its role in ASD development is not known. To address this question we investigate functional consequences of TCF7L2 deficiency in the brain. Evidence from our laboratory shows that Tcf7l2 is highly expressed in thalamus where it regulates the expression of excitability genes. The thalamus is a candidate structure for ASD pathogenesis, as it relays both sensory signals from periphery as well as signals between associative, motivational, executive and motor cortical regions.

We hypothesize that TCF7L2 deficiency in thalamic neurons impairs the activity of thalamo-cortical circuits, whose dysfunctions are common in psychiatric disorders such as ASD. In our laboratory, a mouse strain was created with postanal knockout of TCF7L2 in thalamus. To determine electrophysiological characteristics of thalamic neurons and thalamo-cortical connections in these mice, a series of tests will be performed, including recording of respose to sensory stimulation *in vivo* from thalamus and cortex with Neuropixel probes and patch-clamp. Our preliminary patch-clamp results show decreased excitability of neurons and disfunction of burst mode firing in the knockout strain. Moreover, pilot study of prepulse inhibition *in vivo* showed a lower decrease of inhibited reponse in knockout compared to wild type.

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VALIDATION OF A NEW MOUSE MODEL FOR AUTISM SPECTRUM DISORDER RESEARCH

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Autism spectrum disorder (ASD) embraces several behavioral and sensorimotor alterations. ASD is associated with neurodevelopmental impairments. Considering the important role of thalamocortical connections in processing sensory information and producing behavioral responses, impaired thalamic development can contribute to ASD symptoms. However, this assumption is poorly supported experimentally. Therefore, this study aims to understand the role of the thalamus in the pathogenesis of ASD using a new mouse model, a strain developed in our laboratory in which the regulator of thalamic maturation TCF7L2 is knocked out postnatally. To validate ASD-associated phenotypes, we analyzed the mice's behavioral profile through the following behavioral tests:

Open field, marble-burying test, buried food test, and Eco-HAB. TCF7L2 KO mice present a decrease in social performance, not interacting with other mice during the exploration of a cage and spending less time in the compartment containing social scent. They show a decrease in grooming behavior and no difference in repetitive behavior. In addition, they do not show impairments in locomotor activity or olfactory function, according to the Open field and Buried Food tests. These results corroborate a hypothesis that thalamic dysfunctions originating from perinatal development can be a primary cause of social deficits and behavioral inflexibility in ASD.

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VIRTUAL SCREENING PROTOCOL TOWARDS THE SEARCH OF NEW NON-STANDARD 5-HT7R LIGANDS

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Serotonin receptor 5-HT7, a representative of aminergic family of G protein-coupled receptors (GPCRs), is proved to play important role in a number of pathophysiological process occurring in the central nervous system (CNS), such as depression, anxiety, cognitive disorders, disturbances of the sleep-wake cycle, and schizophrenia. Therefore, it is extensively examined as a drug target in the treatment of various CNS disorders.

The number of already known 5-HT7R ligands is relatively high (there are over 4800 records of compounds with experimentally verified activity towards 5-HT7R deposited in the ChEMBL database); however, due to the relatively high similarity of the 5-HT7R binding site with the binding pocket of the hERG potassium channel, high fraction of 5-HT7R ligands are subject to the risk of displaying cardiotoxicity. The responsibility for the interaction with hERG is mostly put to the basic nitrogen of a compound (which is the main feature of most 5-HT7R ligands).

In the study, we performed virtual screening procedure towards the search of non-standard ligands of 5-HT7R, which do not contain the basic nitrogen atom in their structure. The protocol consisted of application of machine learning methods and docking. Experimental validation of the results indicated several compounds with micromolar affinity to the 5-HT7R.

Funding: The study was supported by the grant OPUS 2018/31/B/NZ2/00165 financed by the National Science Centre, Poland (www.ncn.gov.pl).

MEDICAL SESSION 3

Novel targets in Retinal Ganglion Cell neuroprotection

Symposium organizer: Adrian Smedowski
(*Medical University of Silesia, Katowice, Poland*)

THE ROLE OF RNA-BINDING PROTEINS IN THE RETINAL GANGLION CELLS SURVIVAL

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Increasing evidence suggests that loss of RNA homeostasis is a central feature in many pathological states, including eye diseases. Gene expression is controlled at posttranscriptional level by several factors (e.g., RNA-binding proteins, coding and non-coding RNAs) playing in concert to determine the fate of a given transcript. Among mammalian RNAbinding proteins, the ELAVL (embryonic lethal, abnormal visual system-like) family is a masterpiece of gene expression regulation by affecting RNA metabolism from splicing to translation. The ubiquitous member of this family, HuR/ELAVL1, controls the expression of genes with a key function in physio and pathological contexts. Alterations in HuR/ELAVL1 levels and/or function have been found in some cellular and animal models of age-related ocular diseases. Although the picture is far to be completed, intriguing findings suggest HuR/ELAVL1 involvement in the aetiopathology and its potentiality as a therapeutic target in retinal ganglion cell degeneration.

THE CROSS-TALK BETWEEN ESTROGEN SIGNALLING AND FASR/FASL PATHWAY

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Deficiency of estrogens during the postmenopausal period is an important risk factor for neurodegenerative diseases. Estradiol deficiency can accelerate apoptotic cell death of retinal ganglion cells (RGC), mediated by TNF-receptor family (e.g., FasR/FasL pathway). Since the RGC are part of central nervous system, they are unable to regenerate in case of damage. In the pilot study, we evaluated the impact of surgical menopause on the function and survival of RGC in the rat model of optic nerve crush (ONC). We used 8-weeks old female Long-Evans rats, divided into 2 main groups depending on the time between ovariectomy procedure (OVE) and euthanasia

(2 *vs.* 7 weeks), and subgroups – OVE, OVE+ONC, or ONC. Retinal function was assessed in electroretinography (ERG). RGC loss was evaluated by manual counting using ImageJ software. Seven weeks after OVE, the surgical menopause induced significant retinal interneurons loss, but not RGC loss, however, when the ONC procedure was applied, RGC appeared to be more susceptible to death in estrogens deprivation. In ERG analysis, photopic negative responses were severely diminished in OVE+ONC group. Estrogens deprivation in menopause induced accelerated retinal neurodegeneration that firstly involves retinal interneurons. The lack of estrogens increases susceptibility of RGC to the insult.

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THE MODULATION OF RETINAL SEROTONIN SIGNALLING PATHWAYS USING SELECTIVE SEROTONIN REUPTAKE INHIBITORS AFFECTS THE EXPRESSION OF BDNF AND CONDUCTIVITY OF ELECTRIC SYNAPSES AND PREVENTS RETINAL GANGLION CELL DEATH

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Selective serotonin reuptake inhibitors have shown many antiapoptotic and neuroprotective effects by increasing BDNF content in the retina and by reducing conductivity of electrical synapses, thus limiting secondary neurodegeneration of Retinal Ganglion Cells (RGC) and retinal interneurons (RI).

Fourteen Long-Evans rats were treated orally with Escitalopram or PBS for 12 weeks. After 8 weeks, transient elevation of intraocular pressure was inducted in the right eye in order to induce retinal ischemia (IC). Electroretinography (ERG) was performed in a few time points. Four weeks later, rats were sacrificed and retinas and optic nerves were isolated.

A loss of RGC density was noted in the ischemic retina treated with PBS that was not noticed in the group treated with Escitalopram (261±118 *vs.* 392±92 $p<0,05$). In the Escitalopram-treated group, scotopic amplitudes of all oscillatory potentials (OP) measured in ERG were significantly higher 14 days after IC induction ($p<0,05$), while in the control group deep disturbance of RI function was observed, expressed in significant reduction of OP amplitudes ($p<0.05$).

Oral treatment with Escitalopram prevents desynchronization of RI function during ischemic conditions in a rat model. Observations presented above may become crucial for new therapeutic methods for vascular pathologies of the retina.

HUR SILENCING PROMOTES RETINAL GANGLION CELLS DEGENERATION AND ALLEVIATES THE ACTIVITY OF EXOGENOUS NEUROPROTECTION IN GLAUCOMA

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The degeneration of Retinal Ganglion Cells (RGC) is a common process that with slow rate appears over the time and is related to aging. Additional external stimuli, like ischemia, increased intraocular pressure or inflammation, may accelerate this age-related cell death and, by impairing RGC function, lead to blindness. The neuroprotective mechanisms aim to limit the negative chain-reactions induced by the insult, prolonging the survival of RGC. Interestingly, ELAVL1 protein has been recognized as a regulator factor of most stress response-involved proteins, placing it in the position of a pivotal element in the chain of neuroprotective pathways. We showed that AAV-based silencing of hur gene inclines the retina to senescence in healthy rats, and leads to pronounced RGC death in the glaucoma model. Additionally, we report that intravitreally injected Metallothionein II, which exerts benefits in glaucomatous rat retina, fails to protect RGC when applied in hur-silenced animals.

COMPUTATIONAL SESSION 1

New Methods in MRI

Symposium organizer: Tomasz Pięciak
(*Universidad de Valladolid, Spain*)

DIFFUSION MAGNETIC RESONANCE IMAGING: MAIN APPLICATIONS AND CHALLENGES

Rita G. Nunes

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Diffusion Magnetic Resonance Imaging (dMRI) has become an essential tool both in research and in the clinic, taking advantage of the random motion of water molecules to probe tissue organization at a scale much finer than the achievable image spatial resolution. Although many clinic applications still rely on the basic quantification of the average diffusion coefficient or on mapping the main diffusion orientation with Diffusion Tensor Imaging, this research field has seen many developments since dMRI was first introduced. In this talk I will review some recent research efforts to ad-

dress the limitations of basic dMRI, focusing on potential applications and ongoing challenges.

NOISE RESULTS – LONGITUDINAL SMRI FINDINGS CAN BE LARGELY MISATTRIBUTED TO DIFFERENCES IN DATA QUALITY

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In recent decades magnetic resonance imaging (MRI) has established itself as the golden standard for studying human brain structure and it has become increasingly more important to identify factors that may influence study outcomes and contribute to misleading conclusions. With the regional time-of-day (TOD) differences in structural brain metrics heavily neglected, this work set out to investigate this phenomenon with voxel-based (VBM) and surface-based morphometry (SBM) using the largest longitudinal dataset to date (N=72). VBM revealed ubiquitous and often bilaterally symmetric differences in local grey and white matter volume across multiple areas. The impact of TOD on regional SBM indices was less pronounced. After inclusion of image quality metrics in the models, however, the significant TOD findings were drastically limited. These results suggest that while TOD effect might be present in some regions of the brain, it is image quality that has a much more pronounced impact on experimental results. Nevertheless, both factors should be strictly controlled to prevent false positive findings in longitudinal MRI studies.

TRACT-BASED MAPPING OF BRAIN WHITE MATTER MICROSTRUCTURE ACROSS THE LIFESPAN WITH DIFFUSION TENSOR IMAGING

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Diffusion magnetic resonance imaging is a non-invasive tool depicting directional properties of water diffusion in fibrous tissues such as the brain white matter (WM). The diffusion tractography, a numerical procedure, allows tracking these anisotropic features of the brain and combining them into the trajectories illustrating distant brain regions linkage. As the human brain systematically changes across the lifespan, measuring these connectivity-based alterations becomes an exciting challenge both from neuroscience and clinical views. This work studies the along-track variations and diffusion properties alterations of WM connections due to brain aging based on standard diffusion tensor imaging. The population study aggregates the group of healthy subjects (31F/31M, aged 8-75) scanned with the Connectome 3T Siemens and delivered with the Human Connectome Project. We observe the U-shape mean diffusion properties trajectories of the tract with a rapid elevation (+16.57% for FA) or decline (-13.40% for MD) during adolescence and early adulthood, and a gradual decline (-17.83% for FA) or increment (+12.87% for MD) respectively in adulthood with region-dependent peak between 20y and 35y. Our results suggest that the underlying brain aging-related processes (demyelination or axonal loss) affect brain pathways spatially different and under varying changing rates across the lifespan.

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MR THERMOMETRY OF THE BRAIN: ANALYSIS OF WATER SUPPRESSION IN SINGLE VOXEL SPECTROSCOPY

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In a typical PRESS (Point RESolved Spectroscopy) sequence the water signal is suppressed to allow for metabolite peak quantification. On the other hand, water peak parameters are useful in further metabolite quantification or other specific studies like MR thermometry. Our study compared temperature estimates from two MR spectra with either suppressed or unsuppressed water peaks. We investigated how suppression pulses influence temperature estimates and whether suppressed or unsuppressed water peaks should be used in future MRS thermometry studies. Six calibration datasets were acquired from the phantom. Each uses suppressed and unsuppressed water peaks in conjunction with metabolites: NAA, Creatine, and Choline. *In vivo* data was acquired from 169 healthy adult subjects with PRESS sequence. Two spectra were acquired from each

subject: One before 30 minute fMRI study and one after. Mean brain temperatures (*in vivo*) showed similar significant negative changes between pre and post-fMRI sessions. Comparisons reveal that unsuppressed water data yields higher temperatures and higher deviations overall than suppressed water data. We believe that using suppressed water peak data (where water peak is still visible) is preferable but it is also feasible to use spectra with unsuppressed water peak in conjunction with metabolites from highly suppressed spectral data.

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THE EFFECT OF A NOVEL AQP4 FACILITATOR, TGN-073, ON GLYMPHATIC TRANSPORT CAPTURED BY DIFFUSION MRI AND DCE-MRI

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The glymphatic system is a low resistance pathway, by which cerebrospinal fluid enters the brain parenchyma along perivascular spaces *via* AQP4 channels. It is hypothesised that the resulting convective flow of the interstitial fluid provides an efficient mechanism for the removal of waste toxins from the brain. Therefore, enhancing AQP4 function may protect against neurodegenerative diseases such as Alzheimer's disease, in which the accumulation of harmful proteins and solutes is a hallmark feature. To this day, there have been no proven treatments to enhance the elimination of pathogenic proteins. Here, we test the effect of an AQP4 facilitator, TGN-073, on glymphatic transport in a normal rat brain by employing different MRI techniques. Surgical procedures were undertaken to catheterise the cisterna magna, thereby enabling infusion of an MRI tracer (Gd-DTPA). Before tracer infusion, either TGN-073 or the vehicle were given *via* intraperitoneal injection. Dynamic 3D T1 weighted imaging of glymphatic transport was undertaken over two hours. Further, the apparent diffusion coefficient was measured in different brain regions using diffusion-weighted imaging. We found that rats treated with TGN-073 showed the distribution of Gd-DTPA was more extensive and parenchymal uptake was higher compared with the vehicle group. Water diffusivity was increased in the brain of TGN-073 treated group, which indicates greater water flux. Our results indicate that compounds such as TGN-073 can improve glymphatic transport in the brain. Since glymphatic impairment due to AQP4 dysfunction is potentially associated with several neurological disorders such as Alzheimer's disease, dementia and traumatic brain injury, enhancing AQP4 functionality is a promising future therapeutic target.

COMPUTATIONAL SESSION 2

Novel methods in EEG

APPLICATION OF A MULTIVARIATE MATCHING PURSUIT ALGORITHM FOR THE EVENT-RELATED EEG SIGNALS

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Currently, the most popular approach to the analysis of the event-related components observed in EEG signals in psychological experiments is one based on detailed hypotheses regarding the effects of a priori assumed locations and latencies. We propose a new tool in ERP studies based on multi-channel Matching Pursuit combined with clustering. The algorithm aims to find patterns in EEG signals that are similar across different experimental conditions, but it allows for slight variability in topography and variations in amplitude. The method has yielded the expected results in numerical simulations. Using signals from the emotional categorisation task experiment we showed that the algorithm could be used in two ways. First, the method can be utilised as a specific filter reducing the variability of components, as defined classically, within each experimental condition. Second, equivalent dipoles fitted to items of the activity clusters identified by the algorithm localise in compact brain areas related to the task performed by the subjects across experimental conditions. This suggests that detected activities can be studied as hypothetical hidden components.

RECURRENCE PLOTS, ACTIGRAPHY AND DISORDERS OF CONSCIOUSNESS (DOC)

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Actigraphy, which stands for measuring acceleration of various body parts, is considered a robust method of assessing circadian rhythms. At the same time, one of hypotheses regarding diagnosis of DOC links the state of the patient to the rhythmicity of his movements – as they may reflect restoration of circadian rhythmicity. However, simple methods of circadian rhythms detection failed us in the past due to how complex and diverse are the data gathered from patients. Recurrence plots,

together with quantitative analysis (RQA) are nonlinear methods of assessing dependencies in the data at different time scales and seem promising as a method more sophisticated than standard algorithms used in the actigraphic field. The analysis is conducted on data gathered in the Alarm Clock Clinic in Warsaw. Our exploratory approach focuses mostly on qualitative differences between various stages of DOC which can be observed on generated recurrence plots. Those differences seem very promising, even though the dataset is small and extremely divergent. Standard measures used in RQA allow to cluster one of the stages (Unresponsive Wakefulness Syndrome) – acting like a necessary condition. Altogether preliminary observations made during this study give a glimpse of hope regarding construction of DOC stages classifier based on actigraphic data.

Funding: This research was supported by the Polish National Science Centre (UMO-2018/31/B/ST7/01888).

MACHINE LEARNING REVEALS GENERALISED BRAIN-BEHAVIOR ASSOCIATIONS: A DIMENSIONAL INVESTIGATION OF ERROR-RELATED BRAIN ACTIVITY AND PSYCHOPATHOLOGICAL SYMPTOMS

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Alterations in error processing are observable in a range of anxiety-related psychiatric disorders. For instance, enhanced electrophysiological responses to errors (i.e., error-related negativity; ERN) characterise generalised anxiety disorder while schizophrenia shows attenuated ERN. Diagnostic categories in psychiatry are, however, heterogeneous and numerous studies reported contradictory and non-replicating findings. Thus, precise mapping of ERN to psychiatric symptoms remains unclear. To reveal symptoms central for elevated ERN and error-related positivity (Pe), we recorded electroencephalograms from 171 volunteers (120 F; 41 excluded), aged 18–40, while performing speeded Go/No–Go task and collected scores on 7 questionnaires assessing subclinical symptoms. We applied machine learning methods with cross-validation (N=96) and tested models on a hold-out set (N=34) to identify generalised brain-behavior associations. Our findings indicate that enhanced ERN is associated with rumination (R2=0.068); overestimation of threat (R2=0.055); inhibitory intolerance of uncertainty (R2=0.036). Found associations, however, are significantly less robust than usually assumed. Pe is associated with behavioral inhibition (R2=0.023); rumination (R2=0.063); prospective intolerance of uncertainty (R2=0.044). Our results call for the change in results' validating method to move towards robust findings that reflect stable individual differences and clinically useful biomarkers.

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A COMPARISON OF THE EPILEPTIC DISCHARGES DRIVEN BOLD RESPONSE FUNCTIONS IN EEG-FMRI DATA

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Epilepsy is one of the most common neurological diseases. Using the discharge onset times derived from the EEG signal, one can compute statistical parametric maps (SPM) from fMRI data. It is necessary to prepare GLM regressors by convolving the driving neuronal activity function with the hemodynamic response function (HRF). This work aimed to prepare a MATLAB application that allows EEG-fMRI analysis with different either HRFs or driving functions. Additionally, we compared the results obtained from one patient's data. We proposed 4 different driving functions and 4 models of the HRF. Standard statistical analysis in SPM12 showed activation cluster in thalamus, the voxel showing the maximum statistical value was therefore chosen as the voxel of interest. The BOLD signal from the voxel was extracted and the beta and mean square error values (MSE) were determined for each HRF model using different driving functions. Prepared toolbox enabled efficient processing and analysis of EEG-fMRI data. The calculated beta values and MSE showed differences in the analysis with the use of various regressors. It has also been shown that changing the parameters of the HRF can improve the fit of estimation to the actual BOLD response, which can improve the result of the analysis.

SUPERVISED MACHINE LEARNING APPROACH CAN HELP TO OBJECTIVELY DIAGNOSE PROLONGED DISORDERS OF CONSCIOUSNESS BASED ON RESTING-STATE EEG DATA

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Prolonged disorders of consciousness (pDoC) include unresponsive wakefulness syndrome, minimally conscious state, and emergence from minimally conscious state. The rate of misdiagnosis of pDoC amounts to 40%, mainly due to the difficulty of behavioral clinical diagnosis in that patient group. Methods based on objective evaluation of brain activity may help in establishing a more accurate diagnosis. We have used resting-state EEG evaluation to investigate its diagnostic applicability. The group of 52 pDoC patients were behaviorally diagnosed using Coma Recovery Scale-Revised (CRS-R). The 10-minute resting-state EEG data were transformed into power spectra and then fitted using FOOOF algorithm. The resulting set of features describing spectral composition of the signal (spectral peak frequencies and aperiodic component), obtained from 16 channels comprising frontal, parietal and occipital regions, was examined with a supervised machine learning (ML) Gaussian Naive Bayes classifier. The results demonstrated that the classifier can accurately determine the diagnosis with 75% accuracy with CRS-R diagnosis as reference. Classifier performance was probably impeded by varied pDOC aetiology, lesion location and diagnostic limitations of CRS-R. Further development and refinement of spectral features and ML technique may help to develop an objective pDoC diagnostic tool based on a simple EEG measurement.

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POSTER SESSION 1

IMPACT OF SMALL MOLECULES AND PEPTIDES ON TAU-MICROTUBULES INTERACTION AND TAU AGGREGATION IN PRIMARY PERIPHERAL NEURONS, AND MODELS OF ALZHEIMER'S DISEASE

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Tau protein, a member of the microtubule associated proteins, is found in abundance within the vertebrates' neuronal axons. In fact, Tau is involved in the regulation of microtubules (MTs) polymerization, it is estimated that almost 80% of Tau has close interaction with neuronal MTs. Different Tau conformational changes can lead to pathological Tau aggregations causing abnormal aggregations, which may result in neurodegenerative diseases development, e.g., Alzheimer's disease. Hence, we conducted a comprehended study relating Tau, MTs assembly and neuronal dysfunction using known and novel small molecules. These molecules were examined through *in vitro* experiments on two model neuronal cells: PC12 cells and mice dorsal root ganglia neurons primary culture. Tau protein isoforms were transfected into the neurons with a green fluorescent protein tag. Tau-MTs interaction was monitored in real time using live cell imaging. Moreover, we assessed the small compounds' neuroprotection and cytotoxicity potentials on a human neuroblastoma cell line. In addition, we determined the tendency of those compounds to cross the blood-brain barrier in an *in vitro* model. This study allowed us to determine the dynamic changes in Tau-MTs interaction due to the presence of Tau aggregates and/or the presence of different small molecules, as zampanolide.

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INFLAMMATORY CYTOKINE TNF-A AFFECTS NEURONAL DENDRITIC SPINE DENSITY IN A TAU INDEPENDENT MANNER

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder with two histopathological hallmarks, the accumulation of Aβ peptides and intracellular tau fibrils. In recent years it has been found that inflammation has a key impact in the development of the disease. Tumor necrosis factor-α (TNF-α) is the major cytokine causing inflammation in AD. In this study the effect of TNF-α is investigated on synaptic connectivity in hippocampal organotypic slices in presence or absence of tau using TauKO and B6 (control) mouse models. The slices were treated for 2 h and 24 h with 50 nM TNF-α. Analysis of confocal laser scanning micrographs of dendritic segments were showing a decrease in spine density after 24 h of TNF-α treatment in both genotypes. Indicating that tau has no effect on this spine parameter. Even though there was no tau effect, EpoD, which is a microtubule stabilizing agent, reversed spine density, indicating the involvement of microtubules in TNF-α-induced dendritic spine modulation. The morphology of neurons was not influenced

by TNF-α treatment. Our data suggest, that inflammation induced by TNF-α affects dendritic spines *via* tau independent microtubule modulation.

TARGETING PH-SENSING RECEPTORS IN MULTIPLE SCLEROSIS

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Extracellular acidosis is the main characteristic of inflammatory processes, caused by the increased metabolic demand of infiltrating immune cells. For instance, acidosis is one of the hallmarks of demyelinating CNS lesions in multiple sclerosis. Response to acidic pH is mediated by a family of proton-sensing receptors including OGR1, GPR4, and T-cell-associated gene 8 (TDAG8). While OGR1 plays mainly proinflammatory roles, TDAG8 has anti-inflammatory properties and its immunomodulatory/immunosuppressive effects in oligodendrocytes and astrocytes depend mainly on Gαs activation and cAMP accumulation. We found that the pH-sensing receptors are in disequilibrium in TDAG8 knock-out mice. In the absence of TDAG8, the CNS expression levels of OGR1 and GPR4 are upregulated, thus changing the balance towards pro-inflammatory signalling. TDAG8 receptor is highly expressed in multiple sclerosis demyelinating plaques and its expression is induced by LPS and acidic pH in both oligodendrocytes and astrocytes. The increase of TDAG8 expression is observed also during the process of oligodendrocyte progenitors' maturation. Targeting the TDAG8 receptor with its agonist – rotundine (tetrahydropalmatine) results in a prompt increase of cAMP and induction of calcium signalling.

LIPID-PROTEIN BALANCE IN MAJOR DEPRESSIVE DISORDER – FTIR AND RAMAN ANALYSIS IN POST-MORTEM HUMAN FRONTAL CORTEX

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Major depressive disorder (MDD) is the most common mental disorder in world. Several dozen years of research have resulted in many antidepressants, but there are still no reliable biological markers to help diagnose MDD. Raman and Fourier Transform Infrared (FTIR) spectroscopy provide information on the compounds' chemical structure through the identification and analysis of functional groups. Thus, both spectroscopic techniques were used to determine the quantitative and qualitative changes in the post-mortem frontal cortex collected from psychiatrically-normal control (n=20) and MDD subjects (n=20). In MDD subjects significant changes in the proteins and lipids were observed, therefore, to determine which functional groups depend on each other, correlation test was performed. Symmetric PO2-groups correlated with CH out-of-plane bending vibrations. Correlation between symmetric and asymmetric PO2-groups, was also visible. Moreover CH3 proteins and lipids groups correlated with CH out-of-plane bending vibrations and amide III. In MDD group, higher values of absorbance of peaks corresponding to amides II and I and symmetric PO2-groups were noticed in the brain of men, while in the women's tissue higher values of absorbance originating from asymmetric PO2-groups were observed. Our research has shown that the balance between lipids and proteins in the brains of MDD patients is disturbed.

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FUNCTIONAL IMPAIRMENT IN INDIVIDUALS WITH ANXIETY AND MOOD DISORDERS AND HISTORY OF SUICIDAL BEHAVIOR

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There is increasing recognition of the importance of functional outcomes in patients with mental disorder and suicidal behavior. The aim of this study was to evaluate the severity of functional impairment among patients with anxiety and mood disorders (AMD) with risk of suicidal behavior. This study included 31 (38±12.8 years old, 64.5% women) patients with AMD and high risk of suicidal behavior and 37 controls (42.4±12.7, 81.1% women) (without history of mental disorders, but with physical disability, admitted for physical rehabilitation). There were no significant differences between AMD patients and the control group with respect to age and gender. The Sheehan Disability Scale (SDS) was employed to measure the degree of

the functional impairment in work/school, social life, and home life on 10-point visual analog scale; the sum (SDS-total) was calculated. The mean SDS scores were significantly higher in AMD patients than the controls for social life item (6.84±2.49 *vs.* 0.86±1.27), for family life item (61±2.94 *vs.* 1.35±1.47), for work/school item (6.84±2.66 *vs.* 1.89±2.19), and for SDS-total score (20.29±7.02 *vs.* 4.11±4.31) (all p<0001). Patients with AMD and history of suicidal behavior showed more severe functional impairment than patients with physical disability.

ALTERATIONS IN NRF2 PROTEIN LEVEL IN THE FRONTAL CORTEX OF SUICIDE VICTIMS AND DEPRESSED SUBJECTS ARE ASSOCIATED WITH NF-KB(P65) CHANGES – EVIDENCE FROM POST-MORTEM BRAIN STUDY

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There is evidence for an association between suicidal behavior and major depressive disorder (MDD). Increasing number of studies suggest that cross-talk between nuclear factor-E2-related factor 2 (Nrf2) and nuclear factor-κB (NF-κB) pathway can be crucial for regulation of oxidative stress and inflammation processes in the brain. Our purpose was to investigate the level of Nrf2 and NF-κB (p65) protein levels in whole tissue lysate (WTL) and nuclear fraction (N) of frontal cortex collected from two cohorts: I included 17 suicide victims and 8 sudden-death controls and II contained 23 subjects with MDD and 23 non-depressed controls. The levels of proteins was determined by Western blotting. Our analysis revealed a significantly increased in Nrf2 protein level in the WTL of suicide and MDD subjects, relative to control groups. These alterations were linked with statistically decrease in Nrf2 protein level in N of suicide victims. In turn, in MDD a trend toward decreased Nrf2 protein level was observed. Interestingly, significant increase in NF-κB (p65) protein level of N in cohort I and II have been noticed. Obtained results indicate that the changes in the levels of the Nrf2 and NF-κB proteins may be involved in the pathophysiology of suicide-related disorders (including MDD).

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EVALUATION OF THE GENE EXPRESSION RELATED TO NEURODEVELOPMENTAL PROCESSES AND NEURON-MICROGLIA COMMUNICATION IN APP NL-F/NL-F GENETICALLY ENGINEERED MICE

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In the pathogenesis of Alzheimer's disease (AD), microglia activation is associated with the removal of toxic Aβ deposits, but excessive stimulation may contribute to prolonged inflammation. Appropriate communication between microglia and neurons is essential for controlling microglia activity. Specialized ligand-receptor protein systems are responsible for this, among them CD200-CD200R and CX3CL1-CX3CR1. Both axes are involved in maintaining homeostasis in the brain. They regulate neurodevelopmental processes and are responsible for the normal inflammatory response, while their dysfunction can lead to nervous system disturbances. Using a real-time polymerase chain reaction technique, the expression of the *Cd200-Cd200r* and *Cx3cl1-Cx3cr1* genes in the frontal cortex and hippocampus of APP NL-F/NL-F and control mice was assessed. The mutations were shown to have a significant effect on the expression profile of genes involved in neuronal-microglia communication depending on the brain structure studied and the age of the animals. The changes are dynamic and may be important in AD pathology due to their occurrence at an early stage of animal growth, during a period of increased microglia activation and before the onset of clinical symptoms. Investigating the mechanisms of dysfunction of these regulatory systems may contribute to the development of AD therapy and/or prevention.

WESTERN DIET LEADS TO INSULIN RESISTANCE IN THE BRAIN AND MAY TRIGGER THE DEVELOPMENT OF ALZHEIMER'S DISEASE

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Western diet (WD) is a type of nourishment based on ultra-processed foods. Long-term consumption of

WD leads to disruption of insulin signaling and the development of insulin resistance, which is considered a risk factor for Alzheimer's disease (AD). The aim of this study was to verify that WD can evoke major neuropathological features of AD – amyloid-β (Aβ) plaques and neurofibrillary tangles. To this aim, male C57BL/6J mice were fed WD or standard diet (CTR) from 3 months of age and analyzed at 4-, 8-, 12-, and 16-months of age. The effects of WD on the levels of the insulin signaling pathway components: p-IRS-1(Ser616), p-Akt(473), p-GSK-3β(Ser9), and on AD biomarkers: p-Tau(Thr231) and APP/Aβ levels were assessed in the entorhinal cortex and hippocampus. Entorhinal cortex proved to be more sensitive and revealed an increase in p-IRS-1(Ser616) levels, indicating the development of brain insulin resistance. Moreover, a change in the localization of p-Tau(Thr231) in cellular compartments was observed. We also observed an age-dependent decrease in APP protein levels correlating with the appearance of Aβ peptides under the WD. Obtained results suggest that the WD, by inducing abnormalities in the insulin signaling may be considered as a significant, modifiable risk factor for AD.

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WESTERN DIET – FROM MICROGLIA DYSFUNCTION TO THE ACCELERATION OF ALZHEIMER'S DISEASE PATHOLOGY

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Microglial phagocytosis in the early stage of Alzheimer's disease (AD) plays a beneficial role, however, during disease progression, seems to become insufficient and detrimental, and combined with their pro-inflammatory activity, directly and indirectly impact the main hallmarks of AD in the brain (amyloid-β peptides (Aβ), and tau protein hyperphosphorylation (pTau)). We verified the hypothesis that Western diet (WD) feeding characterized by high level of simple carbohydrates, saturated fatty acids and cholesterol, accelerates microglia dysfunction, what results in deposition of Aβ, tau protein hyperphosphorylation and destabilization of neuronal cytoskeleton. Transgenic mice expressing human APP with Swedish mutation (APPswe) were divided into three age groups. 4- and 8-month-old groups represent early pre-symptomatic stages of AD, while 12-month-old animals represent later stages of AD with visible amyloid pathology. The APPswe mice were fed with WD from 3rd month of age. WD feeding accelerated activation of microglia and its M1 pro-inflammatory polarization profile, and induced dysfunction of microglia phagocytic function (↑Iba1, ↓CD68) in 8-months old mice, what resulted in enhanced production of Aβ plaques and destabilization of neurons in 12-months old mice. These results indicate that the westernized pattern of nourishment is an important modifiable risk factor of AD development.

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DETERMINING THE IMPACT OF MOLECULAR CROWDING AGENTS ON DEPOSITION OF COLLAGEN BY CULTURED MENINGEAL CELLS

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The role that meningeal membranes may play in brain inflammation, and development of pathological changes, is becoming increasingly evident but further knowledge of their biology and 3D environment is vital. The meninges, comprised of dura mater and leptomeninges (arachnoid and pia mater), consist largely of fibroblasts and, in order to create meningeal models, we have used molecular crowding agents (MCAs) to accelerate collagen deposition. By modifying the dilute flask environment (~50 g/L of macromolecules) to mimic the natural, more crowded, cell habitat (~900 g/L), MCAs can greatly enhance modelling of 3D biostructures. Dura mater and leptomeninges were isolated from the skull and brain, respectively, of adult Sprague-Dawley rats and cultured for two weeks. MCA carrageenan (CG) was added at varying concentrations (10 µg-100 µg, three replicates per condition). After 5 days a live/dead assay showed CG had no impact on viability, with >95% alive cells and PicoGreen™ assay for DNA suggested no difference in cell proliferation. However, the alamarBlue™ assay data demonstrated a 75% reduction in metabolic activity in cells treated with 100 µg compared to control ($p<0.05$). Similarly, Hoechst staining confirmed a 34.4% reduction in cell number ($p<0.05$), with no differences in cell morphology between groups, as assessed by vimentin staining.

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HYDROGEN SULFIDE DONOR AP39 PROTECTS HT-22 CELLS AGAINST OXYGEN-GLUCOSE DEPRIVATION

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AP39 as a mitochondrially targeted hydrogen sulfide donor has therapeutic potential in ischemia, but little is known about mechanism of its neuroprotective action. The aim of this study was to investigate the effect of AP39 on neuronal cells under ischemic conditions. HT-22 cells were subjected to oxygen-glucose deprivation (OGD) procedure to mimic ischemic conditions. AP39 (10 nM – 250 nM) was present in the culture medium during OGD (21 h) and reoxygenation (3 h) periods. The control group was represented by HT-22 cells cultured under standard conditions (normoxia and media containing glucose). Cell viability in MTT reduction test as well as the level of extracellular lactate dehydrogenase (LDH) were determined. Cationic voltage-dependent dye JC-1 was used to estimate the mitochondrial membrane potential. Seahorse-based assays were used to study cellular bioenergetics by monitoring oxygen consumption rate and extracellular acidification rate. The obtained results showed a significant beneficial effect of 25nM AP39 on viability of HT-22 subjected to OGD in both MTT and LDH tests and on the mitochondrial membrane potential. Tested compound modulated also cellular bioenergetics. To conclude, AP39 may have neuroprotective effect on cells under ischemic conditions and the mechanism of its action might be associated with modulation of oxidative phosphorylation in mitochondria.

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PHARMACOLOGICAL INHIBITION OF MMP-9 ENZYME ACTIVITY IMPROVES ANIMAL RECOVERY AFTER ISCHEMIC STROKE

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Matrix metalloproteinase-9 (MMP-9) levels are markedly induced after cerebral ischemia. Furthermore, this extracellularly operating protease has been implicated in post-stroke functional recovery. In the present study to evaluate the effects of MMP-9 inhibition on post-stroke recovery, we used PKL-021, a potent inhibitor of MMP-9 and a drug candidate currently under development by Pikralida. For cerebral ischemia we followed focal middle cerebral artery occlusion (fMCAo) protocol in mice. We used animals with genetically modified MMP-9 levels and C57BL6/J mice for control. Mice received 3 doses of PKL-021 during the first 24 h after ischemia. Drug pharmacokinetics was analyzed using mass spectrometry. The minimum effective dose of the drug and inhibitory effect of PKL-021 was determined using Western Blot-base evaluation of MMP-9 dependent cleavage of Nectin-3, its neuronal substrate. We have found shown that PKL-021 administered after ischemic stroke improves animal condition and reduces neurological deficits in wild-type animals as well in MMP-9 overexpressing animals. We have also observed that the drug crosses the blood-brain barrier and is present in the brain after intraperitoneal administration. Notably, PKL-021 inhibited MMP-9-dependent nectin-3 cleavage *in vitro* and *in vivo*. The current study supports the use of PKL-021 as a beneficial component of the post-stroke recovery process.

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SURFACE MODIFICATION OF TIO2 NANOPARTICLES MODERATES NEUROLOGICAL IMPAIRMENTS AND UPREGULATED OXIDATIVE STRESS INDICATOR IN EYES OF ADULT WISTAR RATS

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Titanium dioxide nanoparticles (TiO2 NPs) are widely used in many daily necessities, including medicine, food/beverages, and cosmetics. Besides the numerous benefits of TiO2 NPs utilization, their use raises public concerns since humans are exposed to their toxicity. As different alterations could moderate the observed side effects of commercially available bare TiO2 NPs, we investigated whether TiO2/SA NPs (TiO2 NPs surface-modified with salicylic acid (SA)) impact the bare TiO2 NPs-induced sensory-motor impairments and eye level of 4-hydroxynonenal (HNE) as the final product of lipid peroxidation and indicator of oxidative stress. Our results demonstrate that 14 days following single oral treatment both investigated TiO2 NPs in adult Wistar rats affected neurological functions and promoted oxidative stress to different extents. Namely, the SA modification alleviated TiO2 NPs-induced

asymmetry in four limb movement, while the hind limb clasping reflex and spontaneous activity scores were similar between TiO2 groups. In the eye crude membrane fraction of TiO2/SA NPs-treated rats in comparison to animals treated with bare TiO2 NPs, the HNE level was downregulated. Although SA exhibits the ability to reduce some TiO2 NPs toxicity, due to still unknown mechanism of TiO2 and TiO2/SA NPs actions, further studies are required to verify herein presented findings.

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THE LEVEL OF ACTIVATION OF THE RAT BRAIN NITRERGIC SYSTEM IN RESPONSE TO INDUCED SEIZURES AND THE RELATIONSHIP BETWEEN THE LEVEL OF NO AND THE INTENSITY OF SEIZURE BEHAVIORS

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Epilepsy is a complex disease that involves a diverse set of symptoms and neurological disorders. A conservative model of the imbalance between the excitatory and inhibitory neurotransmitter systems is insufficient to understand the mechanisms of epilepsy. Therefore, it is necessary to include non-classical signaling molecules such as nitric oxide (NO). However, it has not been possible to clearly define whether endogenous NO is a pro or anticonvulsive. The purpose of the study was to determine the temporal profile of changes in the activation of the brain nitrergic system in response to seizures and to correlate the activation of the nitrergic system with the intensity of seizures. The study used a pilocarpine model of epilepsy. The kinetics of NO release was determined by electron paramagnetic resonance spectroscopy followed by NO spin trapping. Seizures were classified on the basis of modified Racine's scale. The data obtained allowed us to determine that after epileptic seizures, intense NO release lasts for the first 12 h. After this, the NO concentration drops sharply to levels that are not significantly different from those in control animals. Additionally, no significant correlation was found between the levels of NO released in the brain and the intensity of seizures.

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BLOCKADE OF H3 HISTAMINE RECEPTORS FACILITATES ANTISEIZURE ACTION OF PENTOXYPHILLINE

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Considering the important role of inflammation in epilepsy development is reasonable to investigate the effects of combined usage of different modulators of neural inflammation. The work aimed to investigate the effects of the blocker of histamine H3 pitolisant hydrochloride (Selleck, USA) and pentoxyphilline (Sigma-Aldrich, USA), which prevents proinflammatory cytokines elaboration upon pentylenetetrazol (Sigma-Aldrich, USA) (PTZ)-kindled seizures in rats. Male Wistar rats four months of age kindled to the stage of generalized tonic-clonic seizure fits with PTZ (35 mg/kg, i.p.) were used in observations. Pentoxyphilline (50 mg/kg, i.p.) administered with pitolisant (5 mg/kg, i.p.) caused the increase of first seizure manifestations latency by 67.2% in comparison with the control group of kindled rats ($P<0.05$). Also, PTZ-induced generalized tonic-clonic fits were prevented, and seizure severity was 1,6+0,2 scored points which were 2.6 times less than the control value ($P<0.01$). Both the latency of first seizures and their severity were significantly different when compared with separate effects of pentoxifylline (100 mg/kg, i.p.) or pitolizant (10 mg/kg i.p.) administrations ($P<0.05$). Also, ictal potentials were absent in the ventral hippocampus under conditions of combined drug administration. Hence, gained data showed that blockade of H3 histamine and endogenous proinflammatory cytokines resulted in synergic antiseizure effects.

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THE MECHANISM OF REALIZATION OF ANTISEIZURE EFFECTS OF CEREBELLAR ELECTRICAL STIMULATION

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We have reported that electrical stimulations of cerebellar structures resulted in the heightened antisei-

zure effectiveness of diazepam against pentylenetetrazol (PTZ)-kindled seizures. Such effects might be explained by the increased antioxidant mechanisms in the brain tissue, which counterparts oxidative stress, as a fundamental pathogenetic mechanism of chronic epileptic activity. The work aimed to investigate the state of antioxidant defense in the cerebral cortex of PTZ-kindled rats under electrical stimulations (100 Hz, 0,25 ms, 50-100 mcA, 2,5 s) of the paleocerebellar cortex (V-VII lobules). Kindling was produced *via* three weeks of PTZ administration (35 mg/kg, i.p.), and animals with fully developed generalized seizure fits were included in the observation. Kindled animals were stimulated two times daily, three days starting 24 h after the last kindled seizure fit, and testing PTZ was administered afterward. The net reduction of superoxide dismutase activity – by 40.7% and catalase – by 32.0% in comparison with the control group of animals registered 24 h after the last sham stimulation. Besides, the level of free thiols in the cerebral cortex was ten times greater than in kindled rats ($P<0.02$). Gained data favoring the role of antioxidant mechanisms as contributing to antiseizure effects of cerebellar ES.

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EFFECT OF KETOGENIC DIET ON THE NEURAL DEVELOPMENT – BEHAVIOR RESEARCH

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The ketogenic diet is a special dietary system that induces a state of ketosis in the body. Many studies indicate that the state of ketosis has a positive effect in the treatment of selected neurological conditions with particular application to drug-resistant epilepsy. This study examines to what extent a ketogenic diet will affect the behavior of young Wistar rats of both sexes in an open field test, which is unique for this type of study. The rats were divided into three dietary groups: ND, a control group on a standard diet; KDND, rats whose mothers were exposed to the ketogenic diet prenatally; and KD, rats that were on the ketogenic diet from conception to 21 days of life (P21). Rats were subjected to the field test twice at P30 and P60. In the case of females at P30, trends can be seen for decreasing distance and increasing resting time where in males there were no statistically significant differences. In contrast, at P60 the changes for females were in resting time, which was lower for the groups on the ketogenic diet. There were no statistically significant differences in males.

PROFOUND ALTERATIONS IN HIPPOCAMPAL LIPID RAFTS FOLLOW *IN VITRO* EPILEPTIFORM ACTIVITY, HYPOXIA AND OXYGEN-GLUCOSE DEPRIVATION

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Seizures and hypoxic-ischemic conditions are brain insults associated to increased risk of epileptogenesis. Lipid rafts, important CNS signalling platforms, may have a crucial role in both synaptic and homeostatic plasticity. We now investigated the alterations in hippocampal lipid raft dynamics that follow such insults *in vitro*. Hippocampal slices from male Wistar rats superfused with aCSF (5% O_2/95% N2) were exposed to 10-min hypoxia (HYPX, 5% CO_2/95% N2) or oxygen-glucose deprivation (OGD, 5% CO_2/95% N2 and partial replacement of glucose by sucrose). Epileptiform activity (EA) was induced by 10-min exposure to 10 uM bicuculine (ictal-like EA) or 30-min superfusion with 0-Mg2+ aCSF (mM: $MgCl_2$, 0; KCl, 6). Lipid raft markers and synaptic markers were evaluated by western blot 50-min following those insults. Flotilin-1, caveolin-1 and gephyrin were markedly reduced following all insults whereas PSD-95 suffered only changes following ictal-like EA and 0-Mg2+ exposure. VGlut1 was very markedly enhanced following HYPX and OGD and VGAT was moderately increased only after OGD. Altogether this suggests a major role for lipid rafts in the early response to seizures and hypoxia/ischemia. These may be related abnormal neurotransmitter signalling, synaptic vesicle recycling or early adaptive synaptic plasticity phenomena following those insults.

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THE EFFECT OF MINOCYCLINE ON SIZE CHANGES IN THE NECROSIS AREA IN CORTICAL MODEL OF PHOTOTHROMBOTIC ISCHEMIC STROKE IN RATS

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Stroke is still a leading cause of death worldwide. In survivors, it can result in long-term disabilityin with various severity ranges. Minocycline, by launching plethora of neuroprotective mechanisms may be beneficial as the treatment. Therefore, it is important to develop new strategies for treating ischemic strokes. Our goal was to examine the effect of treatment on the ischemic area and conditio of motor function in rats. Photothrombotic focal ischemia of motor cortex was produced in 72 male Long-Evans rats. We tested time windows: 12 h, 24 h, 48 h and 7 days . Half of the experimental groups received an intravenous dose of minocycline (1 mg/1 kg b.w/1 ml solution, 10 min after stroke). CatWalk XT, Grip Strength-test and elevated runway-tests were performed. Nissl staining and immunohistochemistryon paraffin scraps were performed. The size, shape and area of the necrosis were measured. In groups with minocycline we observed statistically significant improvement the volume and shape of the necrotic area after an ischemic stroke. The greatest changes were observed in the time groups 48 h and 7 days.

Treatment with use minocycline affects the decrease in the volume of the necrotic area.

HSP70 – DEPENDENT MECHANISMS OF ENDOGENOUS NEUROPROTECTION. NEW TARGET LINKS OF PHARMACOLOGICAL CORRECTION AFTER CHRONIC PRENATAL HYPOXIA

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Prenatal hypoxia (PH) causes pathological changes in the brain and can lead to irreversible long-term disorders of its development and the emergence of neuropsychiatric pathologies in children. The aim of this research was to study the effect of drugs (Angiolin, Thiotriazoline, Tamoxifen, Glutoredoxin, Cerebrocurin, Mexidol, L-arginine and Piracetam) on the expression of HSP70 protein as a factor of endogenous neuroprotection to further substantiate their use in the treatment of prenatal CNS damage in a model of chronic hemic PH. Expression levels of mRNA HSP70 and the content of HSP70 in the cytoplasmic and mitochondrial fractions of the brain of rat on the 60th day of life after PH were determined by real-time PCR and enzyme immunoassay. It has been established that chronic PH inhibits transcriptional processes in neurons and suppresses the synthesis of HSP70. The studied drugs are able to modulate HSP70-mediated mechanisms of endogenous neuroprotection. The most active among HSP70 modulators in conditions of chronic PH are cerebrocurin and angiolin, which outperform other studied drugs in terms of increased expression of HSP70 mRNA and HSP70 protein concentration in the brain of experimental animals and can be considered as promising neuroprotective agents in complex therapy after PH.

CHARACTERISTICS OF INFILTRATING CELLS WITHIN BRAIN HEMATOMA IN A RAT MODEL OF INTRACEREBRAL HEMORRHAGE

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The some studies of the role of endogenous mesenchymal stem cells in the central nervous system recovery after stroke are encouraging. The characteristics of cells infiltrating into a brain hematoma were investigated in this work. The intracerebral hemorrhage was modeled in the right internal capsule, by two-stage injection of autologous blood of 0.02 ml. Hemorrhage area and cellular responses at 1, 3, 10, 30, and 60 days were studied and compared with changes along the needle track in the brain of rats, without blood injection. The degree of hemorrhage and cell infiltration were ranked as points: 1 – small hematoma / single infiltrated cells; 2 – average hematoma / group of cells around hematoma; 3 – large hematoma with neuroinflammation/multiple infiltrates. The CD34, CD44, CD68, CD90 and CD146 positive cells occur in the hematoma with the highest intensity on the 3rd and the 10th day, whereas they are mainly absent on the 60th day. There is no relationship between the intensity of infiltration and the degree of hemorrhage, but a tendency for the appearance of CD44 positive cells in neuroinflammation was noted. Given the fact that mesenchymal cells express the investigated CD markers, we suggest their participation in the recovery processes after a hemorrhagic stroke.

THE INFLUENCE OF THE KETOGENIC DIET ON METABOLIC CHANGES AFTER TRAUMATIC BRAIN INJURY

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The ketogenic diet (KD) is a low-carbohydrate, high-fat diet in which the main energy source are ke-

tone bodies. This diet, used primarily in the treatment of drug-resistant epilepsy, is nowadays considered a therapeutic solution in various neurological conditions, including traumatic brain injury (TBI). The aim of our experiment was to evaluate the effect of KD application after TBI. 27-days-old rats were divided into 2 groups receiving ketogenic or standard diet (SD). Penetrating brain injury was performed at postnatal day 30 in half of the animals from each group. The blood glucose, ketone levels, and body mass were monitored for the following 30 days. The analysis revealed a reduced weight gain in injured KD animals compared to the control group on KD. No such effect was observed for the SD rats. In rats on KD, weight gain was lower than in animals on SD, despite higher caloric intake in the groups on KD. Glucose level was lower in KD rats, however, a keto-adaptation occurred in the control group 19 days after KD introduction, which in TBI rats was observed 14 days later. The conducted experiment shows that TBI is associated with slower keto-adaptation which may indicate systemic changes in glucose metabolism.

PRENATAL STRESS SENSITIZES MICROGLIA CELLS TO LIPOPOLYSACCHARIDE-INDUCED INFLAMMATORY RESPONSE: LINK TO THE IMPACT OF THE FPR2 ACTIVATION

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It has been shown that resolution of inflammation (RoI) is regulated by endogenous molecules, called specialized pro-resolving mediators (SPMs) e.g., lipoxins. SPMs modulate RoI by interacting with specific receptor – Formyl peptide receptor 2 (FPR2). The aim was to investigate if prenatal stress will sensitize an LPS-induced inflammatory response by microglia cells. Moreover, the efficacy of new FPR2 ligands in the modulation of this reaction was estimated. Primary microglia cultures prepared from control and prenatally stressed rats were treated with FPR2 ligands (AMS21, AMS3, CMC23, 0.1 uM) and lipopolysaccharide (LPS; 100 ng/ml) for 24 h. Cell death, NO synthesis and the level of pro- and ant-inflammatory cytokines were assessed. New FPR2 ligands decreased LPS-evoked LDH and NO release in both type of cultures. Moreover, all of the tested FPR2 ligands significantly downregulated LPS-induced IL-1β levels in the control cultures. This effect of new FPR2 ligands on IL-1β levels in "stressed" microglia cells was less visible. All of chosen ligands increased the level of anti-inflammatory cytokine – IL-10. It may be suggested that Priming can influences the activation of the FPR2 receptor and thus RoI, which may lead to altered pro-resolving activity of the new non-peptide ligands used in our research.

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BENZOPHENONE-3 INFLUENCES ON CYTOKINES RELEASED BY MICROGLIA CELLS – *IN VITRO* STUDIES

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Benzophenone-3 (BP-3) is popular UV filter, widely used in cosmetic products. Current data show that BP-3 crosses the blood-brain barrier and suggest that this compound may have an adverse effect on nerve cells. Because one of the causes of neuronal damage is excessive microglia activation, therefore the aim of the study was to assess the effect of BP-3 on viability of primary microglia cells and to evaluate its effect on release of cytokines. Primary microglia cells were isolated from the cerebral cortex of 1-2 days-old rat pups. After 24-72 h exposure of BP-3 (conc. 10-7-10-4M) the compound's cytotoxicity and cells viability were assessed using LDH and MTT tests, respectively. The influence of BP-3 on cytokine secretion under basal conditions and after activation with lipopolysaccharide (LPS) was determined using Luminex technology. BP-3 did not show any cytotoxic effect on primary microglia cells, but significantly increased their metabolic activity. Evaluation of the concentration of released cytokines showed significant changes in their level after exposure to BP-3 and enhancing the LPS-stimulated release of pro-inflammatory cytokines, such as IL-1α, IL-1β and TNF-α. BP-3 has an influence on the activation and polarization of microglia cells and, consequently, may lead to the development of neuroinflammation.

KETOGENIC DIET DOES NOT INFLUENCE HIPPOCAMPAL ASTROCYTES' MORPHOLOGY AFTER INDIRECT KINDLING, BUT INCREASES THEIR RESPONSE TO CHRONIC STRESS

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Reactive astrogliosis, which manifests as an increased level of GFAP (glial fibrillary acidic protein) and astrocytes' processes hypertrophy was proven to associate with the epileptogenesis progression. The aim of our study was to verify the influence of ketogenic diet (KD) on astrogliosis-related changes in hippocampi of electrically kindled rats. Electroshocks were applied by the ear-clip electrodes. Four dietary schemes were applied, including administration of ketogenic or standard feed during the whole experiment or change of the diet on the day of the electrostimulation beginning. GFAP-immunopositive area fraction in hippocampus, as well as astrocytes' morphology, were evaluated. Surprisingly, an increased seizure intensity was noticed in groups receiving KD before the kindling procedure. No morphological changes were observed in response to electrical stimulation, which may result from the use of protocol with a relatively small number of electrostimulations or conducting simplified morphological analysis. We have not observed a significant impact of KD on the number of processes and GFAP immunoreactivity, which may be a result of too short diet application. Increased GFAP immunoreactivity was noticed in KD group with electrodes put on ears during the experiment, which brings us to the conclusion that KD may increase astrogliosis in response to chronic stress.

GLUCOCORTICOID RECEPTORS KNOCK-OUT IN ASTROCYTES INHIBITS CSDS-INDUCED DEPRESSIVE BEHAVIOR

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Glucocorticoids (GCs) are hormones secreted by the hypothalamus-pituitary-adrenal (HPA) axis which regulate multiple physiological processes in mammals, e.g., metabolism. The GC action is largely mediated through regulation of gene expression upon the activation of glucococorticoid receptors (GR). Stress activates of HPA axis, while prolonged exposure results in permanent dysregulation of GR-dependent processes. GR are universally expressed in the central nervous system (CNS), however their transcriptional effects vary across different cell types. In our previous research we showed that astrocytes are an important site of GR-dependent response in the CNS. Here we set out to investigate the behavioral relevance of GR signaling in astrocytes. To this goal, GRs were selectively eliminated from astrocytes of male mice (C57Bl/6J background) using transgenic approach. To induce depressive-like behavior, chronic social defeat stress (CSDS) paradigm was performed, while control animals (CTRL) were housed in pairs. We observed the CSDS elicited expected changes in the anxiety and social interaction of CTRL mice, while these alterations were not observed in mice lacking GR in astrocytes. These results reveal an important role of astrocyte-specific GR signaling in shaping central effects of chronic stress.

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STRESS REGULATION OF FKBP51 IN THE BRAIN: A STUDY IN AN ANIMAL MODEL OF DEPRESSION BASED ON PRENATAL DEXAMETHASONE ADMINISTRATION

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Major depression disorder is a serious public mental health problem with a growing prevalence in the human population worldwide. Despite many years of intensive research, the mechanism of the development of depressive disorders remains unclear, but it is widely believed as a multi-factorial disease caused by the interaction of social, psychological, and biological factors. Accumulating evidence suggests that depression is accompanied by metabolic and endocrine disturbances. Therefore, we investigated the brain level of FKBP51 (negative-feedback regulator of the glucocorticoid receptor, which plays a key role in the stress response), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR) in adult rats exposed to prenatal dexamethasone (DEX) administration and additional acute restrain stress in the adulthood. Our studies revealed the FKBP51 increased level in the frontal cortex of control animals subjected to restrain stress whereas, we did not observe the effect of acute stress on the level of FKBP51 in animals prenatally exposed to DEX. Although we did not show changes in GR and MR levels among examined groups, no increase in FKBP51 in DEX group suggests disturbances in GR inhibition in the frontal cortex. Dysregulation of FKBP51 may explain some of the endocrine changes in the link between stress and metabolic pathways.

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THE EFFECTS OF PRENATAL DEXAMETHASONE TREATMENT ON GLYCOLYSIS ENZYMES IN THE FRONTAL CORTEX OF ADULT MALE RATS

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Depression is one of the most common mental disorders affecting ~5% of adults worldwide, while currently available therapies are not effective in many cases. A lot of studies have been conducted so far to characterize the etiology of this disease, however high heterogeneity of depression makes it difficult. Several factors, including genetic, epigenetic, biological, environmental, and psychosocial determinants, as well as complex relationships between them, are considered to underlie depression.

According to recent studies, metabolic disturbances may play an important role in the pathogenesis of depression. In particular, disruption in glucose metabolism, the main source of energy for brain cells, seems to have a crucial role in the emergence of depression. In order to evaluate this hypothesis, we examined levels of key enzymes involved in the glycolysis, i.e. hexokinase (HK), phosphofructokinase (PFKL), and pyruvate kinase (PK) in the frontal cortex of Sprague-Dawley male rats in an animal model of depression based on prenatal dexamethasone treatment. Our results indicate that prenatally dexamethasone-treated rats, which were subjected to acute stress in adulthood, were characterized by the elevated levels of PFKL and PK, suggesting the intensification of the glycolysis in this brain area.

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AUTOPHAGY IN STRESS-RELATED DISORDERS: ARE POLYAMINES A POTENTIAL NEW TREATMENT OPTION?

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Autophagy is an evolutionary conserved cellular housekeeping process implicated in the surveillance and recycling of cellular proteins and organelles, thereby maintaining cellular homeostasis, performance and metabolism. Importantly, autophagy has been centrally linked to stress-related disorders and mental health. Especially in the brain, synaptic autophagy has been shown to regulate synapse remodeling and plasticity and mitochondrial turnover, which appears critical to neuronal homeostasis and viability, and is directly linked to neuronal functioning. Consequently, genome-wide and proteome-wide association studies have indicated a significant over-representation of impairments of autophagy-related pathways in multiple brain disorders such as clinical depression. In line with these findings, several antidepressants have been shown to induce autophagic pathways. Even though antidepressants are the most effective treatment for depressive disorders, adequate therapy response to a single antidepressant is only observed in 40-60% of patients. Furthermore, plenty of patients show severe drug-related symptoms, so there is still a high demand for novel methods of treatment. Spermidine is a naturally occurring polyamine, which is known to act as an inducer of autophagy and mitophagy. Hence, our research group is interested in investigating spermidine as a potential treatment for clinical depression and other mental disorders. To verify this hypothesis we use different interdisciplinary approaches from cell culture and mouse model to clinical studies in patients and healthy subjects.

THE EFFECT OF VITAMIN D3 SUPPLEMENTATION ON MITOCHONDRIAL ENERGY METABOLISM AND SPECIFIC RECEPTORS CONTENT IN THE HIPPOCAMPUS DURING LONG-TERM DEXAMETHASONE TREATMENT

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Dexamethasone (DEX) is a steroid drug commonly used in medicine with immunosuppressive and analgesic properties. Unfortunately, prolonged DEX exposure significantly affects abnormal brain functioning, causing mood swings, anxiety, and memory disorders. The study aimed to investigate, the effect of vitamin D3 supplementation under chronic DEX treatment on mitochondria energy metabolism and specific receptors content in the hippocampus. The study lasted 28 days and was conducted on 21 male Wistar rats

randomly divided into 3 groups. These included two groups treated by abdominal injection of DEX at a dose of 2 mg/kg/day supplemented with vegetable oil (DEX PL; n=7) or with vitamin D3 600 IU/kg/day (DEX SUP; n=8) respectively, and a control group treated with an abdominal injection of saline (CON; n=6). Hippocampus was collected and weighed immediately after sacrifice. Decreased serum 25(OH)D3 concentration and reduced hippocampal weight were observed in both DEX-treated groups. We found a lower glucocorticosteroid and vitamin D receptors content and disruption of mitochondrial energy function in the DEX PL group. However, supplementation with vitamin D3 abolished these negative effects in mitochondria. Our results clearly indicate that supplementation with vitamin D3 plays a protective role against the effects caused by long-term DEX treatment.

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ANTIOXIDATIVE EFFECT OF VITAMIN D3 ON WHITE MUSCLE DURING LONG-TERM DEXAMETHASONE TREATMENT

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Dexamethasone (DEX) is a widely used broad-spectrum pharmaceutical. Nevertheless, its prolonged or high-dose administration can lead to side effects, including increased oxidative stress in skeletal muscle. One of the agents considered to reduce the adverse effects of DEX is vitamin D3 (VD). The study aimed to evaluate the effect of VD supply under chronic DEX use on levels of free radical damage markers of proteins and lipids. The study was conducted on 20 male Wistar rats divided into 3 groups: saline (n=5), DEX (2 mg/kg/day) + placebo (n=7), DEX (2 mg/kg/day) + VD (600 IU/kg/day) (n=8). Treatment with DEX and VD lasted for 28 consecutive days. Last day of the experiment, animals were sacrificed, and soleus (SOL) and extensor digitorum longus (EDL) muscles were collected and homogenized. The levels of thiol groups and 8-isoprostanes were determined in the homogenates.

Increased 8-iso level was found in both muscles after DEX treatment; nevertheless, VD protected against free radical damage of lipids in EDL. No changes in the thiol group level were observed in both muscles.

During chronic DEX treatment, VD shows a protective effect against free radical damage of lipids in white muscle.

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THE EFFECT OF NATURAL PSYCHOPLASTOGEN 7,8-DIHYDROXYFLAVONE IN ANIMAL MODEL OF DEPRESSION

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7,8-dihydroxyflavone (7,8-DHF) is a natural flavonoid that mimics the effect of brain-derived neurotrophic factor (BDNF). The aim of this study was to determine the effect of 7,8-DHF on nerve tissue changes related to pathological behavioral symptoms in a chronic, unpredicted stress (CUS)-induced model in rats. 12-week-old animals were divided into 3 groups: standard housed rats, rats exposed to stressors, and CUS-rats that received 7,8-DHF (5 mg/kg/day) every 3 days for 3 weeks. We used the forced swim test (FST) and the elevated plus maze (EPM) test to detect behavioral changes. NO-synthase (NOS) activity, protein expression, and concentration of conjugated dienes (CD) were measured. In FST, we found higher immobility in CUS group. CUS resulted in reduction of NOS activity, decrease in nNOS and BDNF expression in mPFC as well as increase in iNOS expression in the hippocampus. 7,8-DHF increased expression of BDNF, nNOS, SOD and TrkB as well as decreased iNOS expression. The concentration of CD was increased after CUS, while 7,8-DHF reduced CD concentration. Our results suggest that increased oxidative state in the brain and reduction of BDNF production may play an important role in the pathophysiology of depression. 7,8-DHF has been shown to have both antidepressant and antioxidant effects.

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PSYCHOSOCIAL CROWDING STRESS AFFECTS THE MRNA EXPRESSION OF SELECTED MOLECULES INVOLVED IN GLUTAMATERGIC AND GABAERGIC SIGNALING IN THE RAT FRONTAL CORTEX

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Disturbances of the glutamatergic transmission in the frontal cortex (FC) are considered one of the core features of stress-related disorders. Little is known which region of FC is affected explicitly by pathological stress and whether GABAergic transmission is involved in these glutamatergic disturbances. Our study aimed to assess the effect of crowding stress (CS) exposure on the mRNA expression of selected glutamate signaling molecules: GluA1, GluN2B, and GABAergic one: parvalbumin, GAD67, GAT1. Analyses were performed in two FC regions: the medial prefrontal cortex (mPFC) and primary motor cortex (M1). Male Wistar rats were overcrowded (70 cm^2 per rat) for 3, 7, or 14 consecutive days while the control (CON) were kept under standard conditions (312 cm^2 per rat). mRNA expression was assessed by the RTqPCR method. We did not see any mRNA changes after 3-day exposure to CS. In comparison to CON, we noted decreased parvalbumin and GAT1 mRNAs in M1, which in the case of GAT1 was visible also in CS14d. GluA1 was upregulated in M1 in the CS7d group *vs.* CON. Our results point out parvalbumin interneurons in M1 as a significant locus of chronic stress evoked signaling alterations.

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EFFECTS OF SELECTIVE LESION OF THE VENTRAL HIPPOCAMPUS AND CHRONIC VENLAFAXINE ADMINISTRATION ON THE BEHAVIOR OF ANIMALS EXPOSED TO THE CHRONIC MILD STRESS MODEL OF DEPRESSION

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Injections of ibotenic acid (IBO) to the ventral hippocampus (vHPC) results in a specific damage that changes in the activity of cortical and limbic neurotransmitters and lead to a range of behavioral impairments that are considered relevant to depression. To determine effects of IBO in vHPC and systemic administration of venlafaxine on behavioral deficits induced by the chronic mild stress (CMS) procedure, male Wistar Han rats were exposed to the CMS procedure for 7 weeks. The efficacy of chronic stress was evaluated in weekly sucose tests. After initial two weeks of stress, animals received acute bilateral microinjections of IBO (5 µg/0,5 µl) into the vHPC, and two weeks later, a 4-weeks administration of the antidepressant venlafaxine (10 mg/kg, IP) was started. The elevated plus-maze (anxiety), the novel object recognition (cognitive deficits) and the social interaction test were conducted. The CMS procedure impaired the animals' behavior in all four tests and these deficits were slightly enhanced by IBO. Venlafaxine attenuated the effect of CMS and IBO on anhedonia, anxiety, and cognitive and social deficits in both control and stressed animals. These data supports the hypothesis that the antidepressant action of venlafaxine restore transmission in the vHPC, which is weakened by IBO lesion in this structure.

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WHAT IS AROUSAL? A DATA-DRIVEN DEFINITION OF AROUSAL

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Arousal is vaguely defined as a brain-body state. Historically arousal has been associated with different neuromodulatory systems, and, in consequence, with different aspects of the general body and brain states. Different measurements have been used as a proxy: from heart rate and respiratory rhythm to skin conductance, or, more recently, pupil diameter. Despite the heterogeneity of measures, arousal is often conceptually seen as uni-dimensional, reflecting an "internal state". While some authors have attempted at bringing attention limitations of the notion of arousal, the term has been and is still widely used: as of February 2022 almost sixty thousand scientific articles mention the term 'arousal' (PubMed). Proper systematization of the concept would require pondering over tens of thousands of individual uses. Here, we use modern natural language processing tools which facilitate the extraction of semantic domains across very large datasets. Using natural language processing we recover semantic clusters within an arousal-related literature data set of ~50.000 abstracts. We complete this analysis with fMRI meta-analysis. Although semantic analysis of the literature seems to point to a heterogeneous, multi-dimensional concept of arousal, fMRI meta-analysis converges on the anterior insula and the amygdala. We discuss the results in light of what we know about these two regions and their involvement on the saliency network.

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mation complète en « sciences cognitives » (l'étude des fonctions mentales supérieures : perception/attention/conscience ; langage ; décision/rationalité ; cognition sociale). Il est situé à l'Ecole normale supérieure (Paris). Number: ANR-17-EURE-0017.

OWL OR LARK? HUMAN CHRONOTYPES AND THE DIFFERENCES IN BRAIN ANATOMY

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Sleep enables many physiological processes and is responsible for maintaining the body's homeostasis. Chronotype is an essential, though often overlooked, variable in neurobiological research. What hours of activity we prefer allows us to define our chronotype and assign us to the groups of "larks", "owls", and "finches". In the search for anatomical differences between the brains of the "larks" and "owls", the author analyzed the MRI scans of 136 people using MATLAB and toolboxes SPM12, CAT12, and xjView. The respondents determined their chronotype using a MEQ questionnaire. In order to visualize the structural differences, the brains were segmented into individual tissues, which made it possible to determine the brain volume and calculate the thickness of the gray matter. Statistical analysis was based on two samples t-test and ANCOVA. Data from the questionnaire, brain volume, age, and sex of the person were considered as covariates. The obtained results of VBM analysis suggest that "larks" have thicker fragments of Broadman area 27 (the parahippocampal gyrus), Broadman area 19 (the lingual gyrus), and cerebellum. Further research is also planned to investigate potential differences in the areas of the brainstem and SCN involved in generating the internal circadian cycle.

LOW GAMMA AUDITORY STEADY-STATE RESPONSE IS SENSITIVE TO THE LEVEL OF AROUSAL DURING NATURAL SLEEP

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In this work, we investigated the specificity of changes in the auditory steady-state response (ASSR) in the low gamma range to various levels of arousal. ASSRs are EEG responses evoked by periodic auditory stimulation. Twelve healthy volunteers were presented with a series of narrow-band chirp stimuli (1000 Hz, chirp modulated 55-25 Hz). Off-line sleep scoring was based on polysomnography data. On EEG data, we evaluated intertrial phase clustering (ITPC) response during wakefulness, N2-NREM, N3-NREM and REM conditions in, respectively 50–44 Hz, 43–37 Hz, and 36–30 Hz frequency bands. We found significant effect of reduced ITPC values from awake to NREM-N3 sleep in the 37–43 Hz band. The comparison between awake and N2-NREM was close to the significance level ($p=0.057$), while there was no significant difference between awake and REM sleep conditions. We found no difference in other frequency bands. These results confirm that low gamma ASSR, specifically around 40 Hz, is particularly sensitive to the level of arousal. The negative finding of lack of difference between ITPC in awake and REM states might also suggest its sensitivity to the presence of the contents of consciousness, however, this finding could be confirmed with dream *versus* no dream contrast.

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HANDEDNESS AND SLEEPING POSITION IN ACTIGRAPHIC SLEEP/WAKE DISCRIMINATION

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There has been an ongoing discussion on whether actigraphy, the measurement of movement, could be used as a reliable method for assessing circadian rhythm (e.g., in disorders of consciousness) or sleep quality. It is agreed that the motion of the wrists may accurately reflect whether a subject is asleep or awake. However, there is no consensus in the literature on whether an actigraph in sleep studies should be worn on the dominant or non-dominant hand. We have analyzed n=7 nocturnal records comprising polysomnography and simultaneous actigraphic signals from both wrists. The discrimination between sleep and wakefulness was obtained *via* the tools for automatic classification — the YASA tool for polysomnography and the Cole-Kripke algorithm for actigraphy. The agreement between both classifications differed between wrists, which led us to the hypothesis that the properties of recorded actigraphic signals might depend more on the preferred sleeping position, rather than on the subject's handedness. Moreover, we have observed that the Cole-Kripke algorithm requires separate parameter calibration for the dominant and

non-dominant hands. However, considering the pilot characteristics of the conducted research and the fact that all of the subjects were right-handed, there is no unequivocal settlement for the discussed issue.

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THE IMPACT OF INCREASING TEMPORAL UNCERTAINTY ON MOTOR PREPARATION AND CONTINGENT NEGATIVE VARIATION

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In the natural environments, sensory events do not always occur at the predicted time, potentially creating temporal uncertainty. How this uncertainty impacts arousal is still unknown. In the present study, we hypothesised that high temporal uncertainty could decrease saliency of future events. This could reduce arousal and the contingent negative variation (CNV) that is a correlate of temporal preparation. Eye movements and EEG were recorded in 42 subjects performing a variable foreperiod task. A central target was briefly displayed, followed by an eccentric one after a variable delay (FP). The task was to gaze at the central target and wait for the eccentric one to make a saccade. In different blocks of trials, the FP variance could be either low (5 ms) or high (120 ms). We found that pupil size and the centrally located CNV preceding visually-guided saccades were reduced in the high uncertainty condition. Maximum velocity of saccades decreased with increasing temporal uncertainty but their latency was only minimally affected. Temporal uncertainty decreased arousal and expectation. This effect could be mediated by a reduced CNV. Contrary to previous results, the impact of the temporal context on the reaction time was reduced, but the responses followed the hazard function.

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SLEEP DEPRIVATION IN THE PERSPECTIVE OF THE DEVELOPMENT OF METABOLIC HEALTH DISORDERS RESULTING IN OBESITY

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The aim of our study was to explore the link between sleep deficit and obesity. In a sleep-deprived state, does the brain reward system activate so easily that it is difficult to maintain discipline when it comes to, for example, refraining from snacking? There is a discounting of time, i.e., a tendency to choose immediate reward over long-term benefit. Based on the literature, the function of food intake can be explained in two ways – eating to satisfy hunger or for pleasure. Overeating, whether driven by hunger or pleasure, usually leads to obesity. We described the functioning in sleep-deficit states of the brain's ‚reward system,' the brain structures responsible for experiencing satisfaction, pleasure and savoring. The study involved a group of 8 participants who were tested after a night of restful sleep and then after a night without sleep. The study consisted of presenting the subjects with a series of appetizing visual stimuli (64 pictures of various dishes) during fMRI recordings. Neural activities in response to stimuli subjectively rated as more or less palatable were examined. The area that showed the most activity was the anterior cingulate cortex (ACC).

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EDUBALL-BASED BRAIN TRAINING: FROM SCHOOLS TO NEUROLABS AND BACK AGAIN

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Studies suggest that incorporating motor-cognitive dual-task exercises into brain training is very valuable. For instance, there are evidences showing that movement-based brain training enhances children's math skills, executive functions, memory processes, and leads to better learning outcomes as well as has a beneficial effect on neuroplasticity. Therefore, researchers recommend combining physical and cognitive tasks in the classroom. So, we create "Eduball", i.e., balls of a smaller size adjusted to the early education pupils with printed numbers, letters, and other characters, used in mini team games at the early school age. In addition to the dual-task issue, Eduball refers to the observation that most types of physical training, such as handball, tennis, judo, etc., are dominated by unilateral motor practice. But to develop the

body and the brain holistically, it is necessary to organize bilateral and non-dominant hand and leg training. Such a striving for symmetry is the main principle of Eduball-based brain training. Here we present the results of 20 years of experiments on the effectiveness of our method. We also demonstrate the prototype of the new version of Eduball, called "mini-Eduball" (the size of tennis balls), which we combine with the neurofeedback and transcranial direct current stimulation methods.

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SMALLER CORPUS CALLOSUM CROSS-SECTIONAL AREA IN ALCOHOL-DEPENDENT MEN WITH MEMORY DISORDERS

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The aim of this study was to determine whether there are main and interaction effects of visuospatial and auditory-verbal memory on alcohol consumption and brain variables such as cross-sectional corpus callosum area in men with alcohol use disorder. Using T1-weighted sequences from a 1.5 Tesla GE Healthcare MRI Optima 360 scanner and a 3.0 Tesla Philips Intera Achieva magnet scanner, the corpus callosum was segmented using yuki form the Automatic Registration Toolbox and volumetric measurements were carried out. The visuospatial and auditory-verbal memory were measured by neuropsychological tests (CVLT and DCS). The 97 men with alcohol use disorder were examined. MANOVA results showed that participants with visuospatial memory disorder had received less education, and had a longer duration of alcohol abuse, more severe alcohol use disorder, and greater alcohol consumption per day. Second, alcohol-dependent men with auditory and visual memory disorders had a smaller total corpus callosum areas. Additionally, among the alcohol-dependent men with memory disorders the smaller rostral body of corpus callosum was determined by the longer alcohol abuse duration. The smaller corpus callosum cross-sectional area significantly affects memory profile in alcohol use disorder, especially have differentiated the patients with normal and disordered memory.

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NEURAL PROCESSING OF EMOTIONALLY CHARGED AUTOBIOGRAPHICAL MEMORIES IN WOMEN WITH MAJOR DEPRESSIVE DISORDER AND BORDERLINE PERSONALITY DISORDER

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Our past experiences are stored in autobiographical memory (AM). Previous studies showed multiple brain regions involved in AM recall in healthy populations, including limbic and occipital cortices. AM recall may be disturbed in clinical disorders, such as depression (MDD) or borderline personality disorder (BPD) in which self-processing is already disrupted. Some studies showed that these patients recall fewer details and tend to recall more negative experiences, however, neuroimaging results are inconclusive. We compared neural processing of sad (SM) and happy memories (HM) in women with MDD, BPD, and healthy control (HC). They were asked to recall and rate the memories during an fMRI session. Subjective emotional state after HMs was less positive in the BPD group than in HC. Within the MDD and HC groups, SMs were less vivid than HMs. AM recall induced robust activations across AM-related regions and these were greater for SMs. Functional connectivity analysis during recall of both SM/HM showed greater connectivity between precuneus, posterior cingulate, and occipital cortex in clinical groups (MDD+BPD > HC), indicating an influence of visual imagery and self-processing on each other during AM recall. As this was the only significant result, these processes may dominate recall in these disorders.

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NEUROFEEDBACK TRAINING FOR LOWERING AGGRESSION LEVEL IN ADOLESCENTS

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Our objectives are to detect and study the effect of neurofeedback-training on the psychophysiological state of teenagers who have high aggression level. Ten schoolgirls 12-13 years old participated in the neurofeedback-training. Each neurofeedback-session took 10 min of targeting increase in alpha-band power in Fz electrode site. We examined the EEG of rest state before and after 10th session of alpha-training. The EEG microstates were calculated for the whole EEG spectra using eLoreta software. Positive effects of neurofeedback-therapy reduce the level of aggression in schoolgirls and increases the power of alpha-rhythm in the central frontal and occipital areas of brain cortex. The electrical activity in girls-teenage before and after alpha-training can be explained by 4 microstates. 47% of the time was described by microstate A, 13% – B, 12% – C, and 28% – D before alpha-training. Microstates A – 21%, B – 15% and D – 48% had highest activity in upper occipital area, microstate C (16%) – in parietal area after 10th session of alpha-training. As a result, microstate A (auditory network) decreases and microstate D (attention network) and C (salience network) increase. Alpha-training had activated a system of attention in girls-teenage and to promoted greater psycho-emotional control in a particular behavioral action.

THE APPLICATION OF FIXEL-BASED ANALYSIS PIPELINE FOR DETERMINING THE IMPACT OF AIR POLLUTION ON BRAIN WHITE MATTER ORGANIZATION – NEUROSMOG

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Brain development is a complex process that starts from the prenatal period through birth, childhood, and adolescence, to adulthood. As reported by recent studies, high levels of urban pollutants may be particularly dangerous to children because they presumably interfere with the brain maturation process, which may lead to neurodevelopmental delay. However, there is still little evidence on associations between white matter microstructure and exposure to pollutants in children. Here, as a part of NeuroSmog project, we present a state-of-art pipeline for investigating how air pollution affects fiber specific metrics of brain white matter organization in children (10-13 years old) with ADHD diagnosis and children from a general population (no ADHD diagnosis). We demonstrate the 1) encountered challenges, 2) preprocess steps including FSL's EDDY tool for correcting eddy currents and movement in diffusion data, 3) data quality assessment using EDDY QC framework, and 4) fixel-based analysis (FBA) pipeline carried out with MRtrix3 toolbox for performing various types of diffusion MRI analyses. This is the first research to apply FBA pipeline to investigate the associations between air pollution exposure and white matter microstructure in children.

Funding: The study is a part of "NeuroSmog: Determining the impact of air pollution on the developing brain" (Nr. POIR.04.04.00-1763/18-00) project which is implemented as part of the TEAM-NET programme of the Foundation for Polish Science, co-financed from EU resources obtained from the European Regional Development Fund under the Smart Growth Operational Programme.

AMYGDALA PARCELLATION USING RECURRENCE QUANTIFICATION ANALYSIS IN PATIENTS WITH COMPULSIVE SEXUAL BEHAVIOR DISORDER

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Compulsive sexual behavior disorder (CSBD) is a mental disorder characterized by the inability to suppress the urge to engage in various types of sexual behaviors. It is speculated that the amygdala may play a huge role in its etiology. Our research aimed to assess whether the amygdala in patients with CSBD can be functionally parcellated into two subdivisions using a pipeline based on recurrence quantification

analysis. To achieve this amygdala parcellation pipeline from the paper by Bielski et al. [1] was applied to resting-state MRI data from 50 CSBD patients and 28 healthy controls (HC). In-house amygdala masks for both groups were created and compared. Adapting the pipeline to our needs, the amygdala was divided into two subdivisions in both datasets. The quality of our parcellations is comparable to the one described in the paper concerning the method. The newly created pipeline is a quick and easily adaptable technique of amygdala parcellation based on brain signal dynamics. Our parcellations will be used as in-house amygdala masks to check whether there are differences in resting-state functional connectivity of the amygdala subdivisions' between CSBD patients and HC.

References: [1]: Bielski K. et al., (2021) NeuroImage 227(117644).

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DISTINGUISHING DIFFERENT TIMESCALES OF UNPREDICTABILITY HELPS EXPLAIN INDIVIDUAL DIFFERENCES IN CHILDREN'S INTERNALIZING AND EXTERNALIZING SYMPTOMS

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Distinct dimensions of early life adversity, such as deprivation, threat and unpredictability have been shown to contribute to the emergence of psychopathology in childhood and adolescence through partially distinct pathways. However, the conceptualization and operationalization of unpredictability is heterogenous in the literature, intermixing variability across widely distinct timescales. In this work, inspired by evolutionary-developmental models of phenotypic plasticity and the cognitive neuroscience of learning under uncertainty, we explored how deprivation, threat as well as short and long timescale unpredictability during early life are related to internalizing and externalizing psychopathology during adolescence. We utilized a structural equation modelling approach to analyse longitudinal data from the Fragile Families and Child Wellbeing cohort. We found that whereas short timescale unpredictability (e.g., experiencing multiple care arrangments on a weekly basis) was primarily related to internalizing problems.

NEUROSMOG: IMPACT OF AIR POLLUTION ON COGNITIVE DEVELOPMENT OUTCOMES IN POLISH SCHOOLCHILDREN – BEHAVIORAL AND MRI STUDY

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NeuroSmog project is focused on investigating the associations between the concentrations of air pollutants and developmental outcomes in schoolchildren, such as attention deficit hyperactivity disorder (ADHD). 744 children aged 10 -13 were recruited across large cities and towns in southern Poland (n=18) with wide-range levels of air pollution. Cases (children with ADHD) were recruited by field psychologists, controls were sampled from local schools. Children were subjected to extensive psychological testing to assess cognitive functioning. To test attentional processes attentional network test and continuous performance test were used. Participants were also scanned using structural, task and resting-state, diffusion-weighted MRI. Main goal is to assess whether logn-term exposure to air pollution affect behavior, function and structure of the brain in both cases and controls. Here we present preliminary results from subsample of 512 children.

Funding: The study is a part of "NeuroSmog: Determining the impact of air pollution on the developing brain" (Nr. POIR.04.04.00-1763/18-00) project which is implemented as part of the TEAM-NET programme of the Foundation for Polish Science, co-financed from EU resources obtained from the European Regional Development Fund under the Smart Growth Operational Programme.

IMPACT OF AGING ON MULTIFRACTAL FUNCTIONAL CONNECTIVITY AND ITS ASSOCIATION WITH COGNITIVE PERFORMANCE: AN EEG STUDY

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Intact brain network function is required for higher-order mental processes, which is known to decline with aging, especially regarding fluid cognitive abilities. Underlying changes in task-related functional connectivity also occur in a temporal scale-free (fractal) manner that has not been characterized yet. Here we investigated the impact of healthy aging on multifractal functional connectivity (MF-FC) derived from resting- and task-state electroencephalography (EEG) recordings and its plausible relationship with cognitive performance. We recruited young (n=21, <45 years) and elderly (n=20, >60 years) participants free of known neuropsychiatric diseases. The measurement protocol consisted of: i) a standardized neuropsychological assessment (Cambridge Neuropsychological Test Automated Battery; CANTAB) and ii) EEG recordings during resting states (eyes open and closed) and during a pattern recognition paradigm administered at three levels of difficulty. To characterize MF-FC, bivariate scale-free exponents and their distribution were estimated from simultaneously recorded EEG signals from which graph theoretical parameters for the corresponding brain network were determined. We found that the elderly group had significantly lower node degrees of brain graph reflecting reduced MF-FC that significantly correlated with measures of pattern recognition memory performance. These findings suggest that age-related changes of EEG-based MF-FC during pattern recognition paradigm predict impaired pattern recognition performance.

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WHICH FACTORS HAVE AFFECTED ANXIETY DURING THE COVID-19 OUTBREAK? A LONGITUDINAL STUDY

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The current longitudinal study aims to identify the factors that have influenced the variance of the level of anxiety state during isolation, anticipatory anxiety, and the factors that have affected the variance of the anxiety trait measured at the beginning and the end of the lockdown. To this end, the subjects (n=495) answered questionnaires assessing anxiety traits (before and after the lockdown), anxiety state (seven repeated measures over the course of 10 weeks), anticipatory anxiety, resilience, experiential avoidance (four repeated measures), as well as the recollection of the isolation period. Data were analyzed with R-type path analysis. The results indicate that the anxiety trait level is significantly lower at the end of isolation, compared to the first measurement, and this decrease is moderated by the emotional reframing of the social isolation period. The anxiety state variance was mainly influenced by the anxiety trait level (1.06) and experiential avoidance (0.23). The anticipatory anxiety was influenced by the anxiety trait (0.23), the experiential avoidance (0.18), living environment (0.13), cohabitation arrangements (0.13), as well as by the way people framed the home isolation time (0.13). The results may suggest intervention in pandemic crises or similar situations.

POSTER SESSION 2

IN SILICO STUDY OF THE CORTICAL NEURON REVEALS VASOCONSTRICTIVE EFFECTS OF COCAINE MODULATES THE FIRING PATTERNS BY INHIBITING SMALL CONDUCTANCE CALCIUM-ACTIVATED POTASSIUM CURRENT

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The vasoconstrictive effects of cocaine modulate the neuronal firing patterns which could contribute to Parkinson's disease (PD). This quantitative study investigates action potential (AP) oscillation patterns of cortical neurons towards the cocaine exposure. This single compartmental in silico model comprises the sodium channel, potassium channel, calcium channel, and calcium diffusion mechanisms. Cocaine exposure (1 mg/kg to 10 mg/kg) profile is reflected as the conductance of small calcium-dependent potassium (SK) channel. First, we simulated the current-voltage profile of the SK ion channel with respect to cocaine stimulus under the voltage clamp protocol. It showed the continuous decrease of outward current because of multiple doses of cocaine from 1 mg/kg to 10 mg/kg. Then, the altered SK ion channel outward current is incorporated into the whole-cell model to investigate the AP firing patterns. The frequency of the firing patterns is elevated for the cocaine dose of 10 mg/kg after the injection of the current stimulus. Few SK ion channels are activated across the membrane and it reduced the whole cell outward current, which elevated the cell's excitability for AP generation. Our *in silico* study suggests the inhibitor of Ca^{2}+ channel as new pharmacological target for bringing the normal firing patterns in cortical neurons, which are affected by cocaine.

INHIBITORY CONTROL OF THE ACTIVITY OF MIDBRAIN DOPAMINERGIC NEURONS BY THE NUCLEUS INCERTUS OF THE BRAINSTEM – ELECTROPHYSIOLOGICAL AND ANATOMICAL STUDIES IN RATS

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The brainstem nucleus incertus (NI) is involved in controlling stress response. Based on our preliminary results, we hypothesized that NI might regulate the activity of the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) – the main dopamine (DA) sources in the brain. Therefore, our study was aimed to investigate the neuronal pathway connecting the NI and the midbrain dopaminergic system in Sprague-Dawley rats. For this purpose, anatomical and electrophysiological experiments were performed. Before electrophysiological extracellular recordings from the urethane-anesthetized male rats were conducted, two viral vectors, one retrograde, carrying Cre recombinase gene, the other carrying Cre-dependent genes for the light-sensitive cationic channel, were injected into animals' VTA/SNc and NI, respectively. To visualize the anatomy of the pathway, retrogradely and anterogradely transported viral vectors carrying genes for fluorescent proteins were injected into the VTA/SNc and NI, respectively. Our anatomical data confirmed the existence of a monosynaptic input from the NI to the VTA/SNc. Furthermore, electrophysiological data showed that a subpopulation of the VTA/SNc neurons (38%) was inhibited by NI optogenetic stimulation. Dopaminergic nature of these neurons was confirmed by juxtacellular labelling followed by immunostaining. Overall, our study shows that NI-originating innervation of the midbrain DA neurons is inhibitory.

DIFFERENT FACES OF NEURONS EXPRESSING DOPAMINE RECEPTORS IN MOTOR CORTEX – THEIR LAMINAR DISTRIBUTION, ELECTROPHYSIOLOGICAL PROPERTIES AND ROLE IN SKILLED FORELIMB REACHING

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Motor cortex comprise the primary descending circuits for flexible control of voluntary movements and is critically involved in motor skill learning. However, due to the complexity of motor cortex circuits, precise mechanisms of motor control and skill learning are still not well understood. Here we have used transgenic mice, electrophysiology and neural tract-tracing methods to target genetically defined cell types expressing D1 and D2 dopamine receptors. We observed that D1+ and D2+ neurons are organized in a separate, largely non-overlapping populations, as evidenced by the laminar distribution of their cell bodies, colocalization and projection patterns. Moreover, based on *ex vivo* patch-clamp re-

cordings we shown that D1+ and D2+ cells have distinct electrophysiological and morphological properties. Finally, we observed that chemogenetic inhibition of D2+, but not D1+ neurons disrupts skilled forelimb reaching in adult mice. These results suggest that dopamine receptor-expressing cells in motor cortex are organized into separate, non-overlapping circuits and that they play specialized roles in fine motor control. We believe that a better understanding of the function of these dopamine-sensitive circuits can be a key to the development of new and more effective therapies for people suffering from neurological disorders.

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DENTATE GYRUS OF THE VENTRAL HIPPOCAMPUS INNERVATION BY BRAINSTEM NUCLEUS INCERTUS – ELECTROPHYSIOLOGICAL AND ANATOMICAL STUDIES IN RAT

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Neuropeptide relaxin-3 (RLN-3) has its primary source in the brainstem nucleus incertus (NI) and NI neurons heavily innervate the dentate gyrus (DG) of the ventral hippocampus (vHPC). vHPC is critically involved in processing stress, emotion and affect related information. Activation of RLN-3 receptors – RXFP3 in vHPC promotes social avoidance and anxiety, however, the neuronal mechanisms underlying NI-vHPC interactions are still little understood. Therefore, these studies aimed to verify the nature of vHipp neurons sensitivity to RXFP3 activation and to map the distribution of NI-originating and RLN-3 containing fibers within vHPC. Results of the whole cell patch-clamp studies showed an inhibitory effect of RXFP3 activation on the activity of DG vHipp interneurons, which implicates an excitatory effect of RLN3 on DG granule cell activity. Viral-based, neural tract-tracing revealed a high density of NI-originating fibers within the polymorphic and molecular layer of the vHipp DG. Importantly, majority of NI originating fibers were RLN3-positive, what indicates NI as a main RLN3 source in the vHipp. The presented results prove the existence of a functional link between NI and vHipp, and indicate NI-vHipp axis as an important element of the neural mechanism involved in stress and arousal related information processing.

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THE EFFECTS OF RXFP3 RECEPTOR ACTIVATION ON NEURONAL ACTIVITY OF THE RAT VENTRAL HIPPOCAMPUS – *EX VIVO* STUDIES

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Anxiety disorders are one of the most common mental disorders. Regardless of their global prevalence, the underlying neuronal mechanisms are still not fully understood. Therefore, further research and novel approaches are crucial for enhancing treatment options. One of the structures controlling anxiety related behaviors is the ventral hippocampus (vHipp). The vHipp is strongly innervated by the stress-sensitive nucleus incertus (NI), the main source of neuropeptide relaxin-3 (RLN3) in the brain. Importantly, the activation of the RLN3 receptor – RXFP3 in vHipp neurons has been shown to promote anxiety and social avoidance. Nevertheless, the neuronal mechanisms of RLN3/RXFP3 signalling in the vHipp remain unclear. Therefore, with the use of multi-electrode array recordings *ex vivo*, we aimed to determine the impact of RXFP3 activation on neuronal activity of the rat vHipp dentate gyrus (DG). Our recordings revealed both inhibitory and excitatory effects on vHipp DG network activity. In addition, using fluorescent multiplex *in situ* hybridization we showed that majority of vGAT1 mRNA-expressing cells in the vHipp GC simultaneously express RXFP3-mRNA. The density of RXFP3 mRNA and the high sensitivity of DG neurons to RXFP3 activation suggest that the NI-vHipp pathway plays a major role in the control of anxiety.

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REAL-TIME IMAGING OF DOPAMINE RELEASE AND NEURONAL POPULATIONS DYNAMICS IN THE MOTOR CORTEX OF AWAKE MICE – DECODING OF REWARD-RELATED SIGNALS AND MOVEMENT PARAMETERS

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Motor cortex comprise the primary descending circuits for flexible control of voluntary movements and is critically involved in motor skill learning. One possible process by which motor learning and updat-

ing is accomplished involves dopaminergic modulation of local neuronal activity. However, causal relationship between dopamine release and neuronal activity in the motor cortex has not been directly tested. Here we have performed dual-color fiber photometry recording of dopamine release and local neuronal activity with genetically encoded sensors, GRAB_DA2h and jRGECO1a, in the motor cortex. Head-fixed animals were trained to use their forelimbs to reach for, grab and manipulate joystick in order to obtain water reward. We observed an increase of GRAB_DA2h and jRGECO1a fluorescence during joystick movement and water consumption. To further determine which brain structures are innervated by cortical dopaminoceptive neurons, we counted retrogradely labeled cells expressing dopamine receptors in the motor cortex. Our preliminary results suggest a relationship between dopamine release and local activity of dopaminoceptive neurons in movement initiation and signaling the outcome of an action. We believe that the better understanding of the function of neural circuits involved in motor learning is crucial for developing novel and more effective therapies for people suffering from neurological disorders.

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CHARACTERISTICS OF THE RESPONSE OF THE RAT NUCLEUS INCERTUS NEURONS TO A STRESSFUL STIMULUS – ELECTROPHYSIOLOGICAL AND BIOCHEMICAL STUDIES

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Among the brain structures involved in stress response, the brainstem nucleus incertus (NI) plays an important role. Although studies showed an indirect involvement of NI in controlling stress responses, the comprehensive description of the mechanism behind it is unknown. Therefore, our study aimed to investigate NI neurons' responsiveness to aversive stimuli in Sprague-Dawley rats. For this, electrophysiological and biochemical experiments were performed. During electrophysiological experiments, the activity of NI neurons was extracellularly recorded from urethane anesthetized male rats exposed to aversive stimuli. Simultaneously, field potential was recorded from hippocampus (hipEEG) to monitor brain state alternation evoked by urethane. To study the involvement of this brain circuit in freely moving animals, an aversion-inducing behavioral protocol followed by c-Fos immunostaining was performed. Electrophysiological data showed that the majority of NI neurons were excited by aversive stimulation, however, a few of them were inhibited. Interestingly, we identified a group of NI neurons which response switched (i.e., from excitation to inhibition) when the brain state was changed. Accordingly, our immunohistochemical studies confirm that the activity of NI neurons was elevated when the animals experienced aversive stimulation in an operant chamber. Overall, our study shows physiological mechanisms by which NI controls the stress response.

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IMPACT OF ELASTIN DERIVED PEPTIDES ON NEUROSTEROIDS PRODUCTION IN CELLS *IN VITRO*

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Astrocytes play a key role in the steroidogenesis which is based on producing of the cholesterol, progesterone, testosterone, and/or estradiol. Degradation products of elastin, called elastin-derived peptides (EDPs) are detectable in cerebrospinal fluid and its number increase during aging. VGVAPG peptide is conservatively present in elastin and EDPs. Therefore, the aim of this research was to investigate the impact of VGVAPG peptide on the production of neurosteroids markers in mouse astrocytes *in vitro*. Primary mouse astrocytes were maintained in DMEM/F12 without phenol red, and supplemented with 10% charcoal/dextran-treated fetal bovine serum. To elucidate the mechanism of the VGVAPG peptide action in astrocytes, cells were exposed to 10 nM VGVAPG peptide and co-treated with agonists and/or antagonists (3-methyladenine, PP242, atorvastatin, lactose, rosiglitazone, GW9662 and c-Src kinase inhibitor I) of different cellular receptors. After cell stimulation, the production and secretion of progesterone, testosterone, and estradiol were measured by ELISA method. The results showed that after treatment of astrocytes with VGVAPG peptide the changes in the production and secretion of progesterone, testosterone, and estradiol were noticed. However, due to preliminary character of our data more research, underlying the mechanism of VGVAPG peptide action in nervous system is needed.

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THE ROLE OF PERINUCLEAR MAKAP SIGNALOSOME IN THE REGULATION OF NFAT FUNCTION IN PRIMARY RAT HIPPOCAMPAL NEURONS

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Muscle A-kinase anchoring protein (mAKAP) is a scaffold protein localized to the nuclear envelope of neurons and striated myocytes, but the function of neuronal mAKAP has not been well-characterized. mAKAP binds a large number of enzymes involved in cell signaling, including calcium-dependent phosphatase calcineurin (CaN) which is an upstream activator of nuclear factor of activated T-cells (NFAT). Despite the critical role of NFAT-dependent transcription in neurons, it is not known how the activity of these transcription factors is regulated. By binding both CaN and NFAT, mAKAP signalosome is hypothesized to regulate NFAT nuclear translocation and NFAT-dependent transcription critical for neuronal survival and axonal outgrowth. We confirmed mAKAP expression and mAKAP-NFATc4 interaction in primary rat hippocampal neurons using Western Blot and co-immunoprecipitation techniques. Moreover, the association of NFATc4 with mAKAP signalosome is enhanced during neuronal depolarization and depends on the activity of calcineurin. Thus, mAKAP located in the perinuclear space may be a critical point for NFATc4 activation and nuclear translocation. In this process, mAKAP-dependent NFATc4 dephosphorylation seems to play an important role.

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MATERNAL HIGH-MONOSACCHARIDE DIETS CHANGE BEHAVIOR AND MELANOCORTIN TYPE 4 RECEPTORS EXPRESSION IN RAT OFFSPRING

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Sugar is an important energy source for proper organism homeostasis and is a highly palatable dietary factor. Clinical and preclinical studies have indicated that excess maternal sugar consumption predisposes to offspring metabolic distribution, but little data point to mental disorders development. The aim of our studies were to examine the impact of maternal high-monosaccharide diets (HMDs), during pregnancy and lactation periods, on the offspring's behavioral responses and melanocortin type 4 receptors (MC-4R) expression. Adolescent and young-adult offspring Wistar rats of both sexes after maternal, rich in glucose or fructose, diets were tested in locomotor activity, the novel object recognition, the elevated zero maze, and the forced swimming tests. The *MC-4R* gene expression and protein level were measured, using RT-qPCR and ELISA, in several offspring's reward system brain structures at postnatal days 28 and 63. The behavioral observations showed that maternal fructose diet prone to anxiety-like behavior, and increased preferences for curiosity in males. Moreover, HMDs affected at the level of MC-4Rs mRNA and protein depending on the offspring's sexes and ages. Our results showed that perinatal offspring exposure to the maternal HMDs can be a predictor of the development of nervous or/and mental disorders and changes in melanocortin system regulation.

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THE EXCITABILITY AND REACTIVITY OF 5-HT1A RECEPTORS IN DORSAL RAPHE NEURONS OF 5-HT7 RECEPTOR KNOCK-OUT MICE

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The serotonergic system in the brain is controlled by regulation of firing of dorsal raphe nucleus (DRN) serotonin (5-HT) projection neurons. 5-HT1A (the target of many antidepressants) and 5-HT7 receptors play a particularly important modulatory role in the DRN. Since these two receptors have opposing effects on neuronal excitability and can directly interact within the cell membrane, it is of interest whether the absence of one would affect the activity of the other. In this study we compared the excitability of 5-HT DRN projection neurons and their response to 5-HT1A receptor activation in wild-type (wt) and 5-HT7 knock-out (5-HT7KO) mice. DRN slices were prepared from adult male 5-HT7 KO or wt mice and whole-cell recordings were obtained from DRN neurons. 5-HT cells were distinguished from other neurons based on the shape of the action potential and their identity was further confirmed by immunostaining for biocytin and tryptophan hydroxylase. To measure neuronal intrinsic excitability, the gain of each cell was calculated based on current-firing frequency relationship. 5-HT1A receptors were activated by bath-applied

5-carboxyamidotryptamine (5-CT; 1 μM, 2 min). The results show no statistically significant differences in intrinsic excitability and 5-HT1A-dependent currents between 5-HT DRN neurons of wt and 5-HT7KO mice.

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EXPRESSION OF THE *OPRM1* GENE IN THE MOUSE STRIATUM

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The μ opioid receptor in mice is encoded by the *Oprm1* gene. Multiple transcript variants of the gene were identified, products of alternative splicing, two possible transcription starts, and several termination signals. Altogether, about 30 distinct variants encoding several isoforms were reported as possible. Here, we investigated the expression of various transcriptional forms of *Oprm1* in the striatum of C57BL/6N mice. We analyzed the results from a long-read Oxford nanopore sequencing together with the data generated by Visium spatial transcriptomics. We established that the most abundant transcript contains exons 1 to 4 and an unexpectedly long, 10 kb 3'UTR in the qA1 region of chromosome 10. To confirm the result, we performed RNAscope *in situ* hybridization with a customized probe targeting the 3'UTR region. The sequencing also revealed the presence of some variants lacking exon 4, albeit their abundance seemed relatively modest. In conclusion, our data suggest that a dominant, previously not reported *Oprm1* transcript in the murine striatum represents approximately 90% of total expression. In our future research, we would like to examine the distribution of the transcripts in other brain regions and potential implications of the long 3'UTR.

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THE ENDOGENOUS OPIOID SIGNALING MODULATES SOCIAL MEMORY IN MICE

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Here we investigate how endogenous opioid signaling controls social recognition in mice. We have used two strains of genetically modified mice with deletion of the genes encoding the two main precursors of endogenous opioid peptides prodynorphin (Pdyn) and preproenkephalin (Penk). Male and female mice of both strains had no apparent impairments, showed normal activity in the open field test and no change in anxiety-like behaviors. Interestingly, both strains expressed normal preference of saccharine-sweetened water, and did not differ in the volume of liquids consumed. The mutations had no appreciable effects on the amount of time spent in interaction in the open field with a novel partner, thus indicating normal social anxiety and/or sociability. However, in the test for social memory, animals lacking the *Penk* gene showed significantly increased social interaction time with a previously encountered partner. Conversely, social memory appeared intact in mice with the Pdyn mutation. Taken together, these data replicate some of the previously reported phenotypes in Penk and Pdyn KO mice, though we would like to note that, contrary to previous findings, no evidence was found for altered-anxiety like behaviors or preference for sweet taste. The potential change in social memory could be in line with the proposed role of opioid signaling in social behaviors, though this requires further validation.

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THE EFFECT OF ACUTE KETAMINE OR PSILOCYBIN ADMINISTRATION ON RATS ACCUMBAL NEUROTRANSMISSION AND BEHAVIOR

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Recently, both ketamine and psilocybin have been studied as rapid-acting antidepressants. The former acting as NMDA receptor antagonist, the latter binding to various 5-HT receptors, both induce alterations in mood and perception. The nucleus accumbens (NAc) as an inherent part of the limbic system has long been considered as one of the key brain regions concerned in affective disorders. The aim of this study was to observe the effects of acute ketamine or either low or high dose of psilocybin on rat neurotransmission in the nucleus accumbens and rats locomotor activity and anxiety-like

behavior. The study was conducted on male Wistar-Han rats (280-300 g). The animals were treated with single dose of ketamine (10 mg/kg) or psilocybin (2 or 10 mg/kg). The accumbal levels of dopamine, serotonin, glutamate and GABA were measured using microdialysis in freely moving animals. The effect on behavior was assessed with light/dark box test. Acute administration of both ketamine and psilocybin elevated extracellular levels of all neurotransmitters except glutamate; in this case ketamine increased its level, while both doses of psilocybin decreased it. Both substances affected locomotor behavior. What is more, psilocybin exhibited weak, but significant anxiogenic effect.

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IMPACT OF KETAMINE ANESTHESIA USED DURING STEREOTAXIC SURGERIES ON LATERAL HABENULA ACTIVITY OVER *IN-VIVO* ELECTROPHYSIOLOGICAL EXPERIMENTS

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Ketamine-xylazine anesthesia is widely used in laboratory animals. Despite that, the long-lasting effects of ketamine in the dose necessary to induce anesthesia are not considered. Ketamine has been also known as a substance of antidepressive potential due to reduction of hyperactivity in lateral habenula. Considering the above, I decided to examine the effect of ketamine administered during stereotaxic surgeries on lateral habenula activity over *in-vivo* electrophysiological recordings. To do that, multi-electrode array recordings (MEA) under urethane anesthesia on adult Sprague-Dawley male rats were conducted 2,5 – 4 weeks after ketamine-xylazine injections. My research indicates that ketamine used in the dose necessary to induce and sustain anesthesia, leads to the reduction or even silence of the spontaneous activity of lateral habenula during electrophysiological recordings. The above results suggest that ketamine should not be used throughout surgeries preceding experiments in which lateral habenula and potentially other structures e.g., ventral tegmental area or raphe nucleus, are tested. My research also indicates that more emphasis should be placed on learning about the long-lasting effects of specific anesthetic substances. It will enable to receive more reliable research results and reduce sacrificed laboratory animals.

HBK-10, A 5-HT1A AND D2 RECEPTOR ANTAGONIST, SHOWS ANTIPSYCHOTIC-LIKE ACTIVITY IN MICE

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Schizophrenia affects around 24 million people worldwide. In addition to positive and negative symptoms, the majority of patients suffer from cognitive impairments and anxiety that worsen their quality of life and remain a big challenge to treat. Therefore, it is substantial to develop novel compounds with antipsychotic-like properties that would also improve memory deficits and anxiety associated with schizophrenia. As our previous studies proved that a novel 2-methoxyphenylpiperazine derivative, HBK-10, showed a high affinity for 5-HT1A and D2 receptors, here we investigated its antipsychotic-like, anxiolytic-like, and anti-amnesic properties. In all experiments, we used male CD-1 mice. We performed an amphetamine-induced hyperlocomotion test to determine the antipsychotic-like activity of HBK-10. To assess the cataleptogenic potential of the tested compound a catalepsy bar test was used. Next, we investigated the anxiolytic-like properties in a four plate test. To determine the possible anti-amnesic activity of HBK-10, we induced memory deficits by MK-801 injection and then tested the compound in a novel object recognition test. HBK-10 presented antipsychotic-like activity in mice. Importantly, the compound did not induce catalepsy in a wide dose range, which suggests its low potential to cause extrapyramidal symptoms. However, HBK-10 neither displayed anxiolytic-like activity nor reversed MK-801-induced recognition memory impairments.

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SENSORY DISORDERS IN ASD – TEST IN BTBR MOUSE MODEL OF ASD

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Despite affecting almost all ASD patients, sensory disorders were treated as a secondary outcome of general

developmental impairments. Currently, the hypothesis that changes in sensory systems are primary to the developmental disorders and neurobiology of ASD is increasingly being considered. There is a need for reliable tests checking sensory sensitivity in mouse models of ASD. We aimed to verify two behavioral tests in BTBRT+Itpr3tf/J mice (model of autism) as compared to a control (C57BL/6J). First, we used ecological, automated experimental cages (IntelliCage) with drinking corners labeled with multi-sensory or light stimuli. We compared the numbers of visits to given corners. In the second experiment, mice were subjected to a whisker nuisance test (WNT), during which the animals' vibrissae were stimulated with a wooden stick. We compared the average time spent by the mouse on the behaviors indicative of aversion and/or irritability. Preliminary results of our studies indicated elevated tactile reactivity in BTBR mice in WNT, with no difference in respect to sex; and tendency for stronger avoidance of stimulated corners in the IntelliCages. However, the experiment also highlighted the importance of a stable control group, as the two runs of IntelliCage tests indicated divergent C57 behavior.

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EVALUATION OF ADAPTIVE CHANGES IN IONOTROPIC GLUTAMATERGIC RECEPTORS INDUCED BY ANTIDEPRESSANT TREATMENT

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For many years of research into depression, scientists focused primarily on the studies of changes in the cerebral cortex and the hippocampus. However, recent investigations suggest a cerebellar role in the pathophysiology of depression and the mechanisms of antidepressant drug action. Yet, the study of this structure has mainly been of neuroimaging nature. There is little data on the biochemical changes occurring in the cerebellum in the course of depression or its treatment. Our previous data showed the adaptive changes in the rat cerebellum induced by the 21-day administration of antidepressants concerning ionotropic glutamatergic receptors. Our experiment aimed to investigate if the adaptive changes in the rat cerebellum occur after shorter, 14 days of antidepressant administration. Drugs with varying mechanisms of action were selected: imipramine, reboxetine and S-citalopram. As a control, saline was used. Drugs were administered to rats (n=8/group) intraperitoneally for 14 days. Cerebellums were isolated, and protein expression was determined using Western blot analysis. The study involves the GluN2B subunit from NMDA and GluA2 subunit from AMPA glutamatergic receptors. Preliminary results show adaptive changes in NMDA subunit concentration after reboxetine and S-citalopram administration.

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REVERSIBLE INHIBITION OF THE OLFACTORY BULB REDUCES MK801-ENHACED HIGH-FREQUENCY OSCILLATIONS (130-180 HZ) IN THE PIRIFORM CORTEX

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In rodents, NMDAR antagonists enhance high frequency oscillations (HFO) 130-180 Hz measured in LFP in many brain regions. The olfactory bulb (OB), a strong generator of HFO, sends excitatory projections to the piriform cortex (PCtx). Here, we examined whether systemic injection of MK801 also enhances HFO in the PCtx and if reversible inhibition of the OB influences this activity. LFP from the OB and PCtx were recorded after systemic injection of 0.15 mg/kg MK801 in freely moving rats. Thirty minutes after injection rats received microinfusion of muscimol (0.5 μg) or saline to the OB or PCtx. Systemic injection of MK801 increased the HFO power in both structures. HFO power was significantly higher in the OB compared to the PCtx. Microinfusion of muscimol to the OB produced an immediate reduction in HFO power in the OB and PCtx. By contrast, muscimol infusion to the PCtx produced a gradual reduction in HFO power in the PCtx without affecting the OB. These findings suggest that OB efferent activity plays a critical role in the generation of HFO post NMDAR antagonists in downstream targets. The OB appears to play a crucial role in broadcasting this activity to other brain areas.

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OXYTOCIN RECEPTOR AGONIST LIT-001 REVERSES IMPAIRMENTS IN THE NOVEL OBJECT RECOGNITION TASK IN THE NEURODEVELOPMENTAL SCHIZOPHRENIA MODEL

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Schizophrenia is a chronic, debilitating disease of uncertain etiology with strong neurodevelopmental compound. Researchers distinguish three clusters of symptoms: positive (psychosis), negative (social withdrawal, depression) and cognitive (impaired learning and memory). Oxytocin (OXT) is a neuropeptide involved in social functions, including social memory and deficits in oxytocin's production or secretion are present, among others, in depression and schizophrenia. Previous studies on exogenous OXT administration to schizophrenia patients have provided inconsistent results. First nonpeptide OXTR agonist, LIT-001 may bring a breakthrough in the oxytocin studies due to its better penetration of brain tissue. The schizophrenia model was obtained by intraperitoneal administration of mitotoxin methylazoxymethanol acetate on GD 17 to pregnant rat dams. Offspring of such treated dams were tested in early adulthood in the novel object recognition task (NORT) to evaluate pro-cognitive effects of LIT-001. Animals received intraperitoneal injection of LIT-001 (1 mg/kg) or vehicle either for 9 days before test or 30 min prior to the first phase of the NORT. Results suggest that LIT-001 can reverse cognitive deficits present in the MAM model of schizophrenia, improving animal performance in NORT. As oxytocin is mainly involved in social activities, the efficacy of the OXTR agonist against MAM-induced social dysfunctions warrants further studies.

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EVALUATION OF NEUROPROTECTIVE POTENTIAL OF 5-HT7 AGONISTS IN CELLULAR MODELS OF PARKINSON'S DISEASE

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Serotonin (5-hydroxytryptamine, 5-HT) is a crucial neurotransmitter regulating a wide range of physiological and pathological functions. Among 5-HT receptors widely distributed in the brain is the 5-HT7, the stimulation of which favors neurite outgrowth. Since the role of 5-HT7 in neuroprotection is not well recognized, we studied the effects of commercially available 5-HT7 agonist, 5-carboxamidotryptamine (5-CT) and low-basicity 5-HT7 agonists (AH-494, AGH-238 and AGH-194) in cellular models of Parkinson's disease. We used human neuroblastoma SH-SY5Y cells exposed to oxidative stress inducer (hydrogen peroxide, H2O2) or PD neurotoxins, 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenylpyridinium (MPP(+)). We have shown that a 30 min pretreatment with 5-CT (0.01 and 0.1 uM), AH-494 (0.01 and 0.1 uM) and AGH-238 (1 uM) but not with AGH-194 partially attenuated the H2O2-evoked cell damage in undifferentiated (UN-) SH-SY5Y cells. We did not find any protection by these compounds in retinoic acid (RA-) differentiated SH-SY5Y cells suggesting that some mechanisms of its protective action could be masked by RA. Moreover, the studied 5-HT7 agonists (0.01-1 uM) have shown no protective efficacy against 6-OHDA or MPP(+)-evoked cell damage in both cell phenotypes. Our data point to a limited neuroprotective efficacy of 5-HT7 agonists in human neuroblastoma cells used as neuronal-like model.

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LENTIVIRAL DELIVERED CRISPR-CAS9 SYSTEM FOR MECHANISTIC INVESTIGATION IN PRIMARY NEURONAL MODEL OF PARKINSON'S DISEASE

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Parkinson's disease is a neurodegenerative disorder characterized by loss of dopaminergic neurons and accumulation of protein aggregates called Lewy bodies which mainly consist of α-synuclein. We developed and validated lentiviral-vector mediated CRISPR-Cas9 system to knock-out specific genes in neuronal model of αsynuclein aggregation. SgRNAs targeting Akt1, Src and Tmem175 were designed and cloned with type IIs restriction enzymes into 3rd generation lentiviral transfer plasmid. Cloned vector expressed sgRNA under human U6 promoter, SpCas9 and mCherry both under human synapsin promoter. Lentiviral vectors were packaged in HEK293T cells. To determine effectiveness of gene ablation, DNA from transduced primary neurons was isolated after 3, 7 or 10 days, region spanning sgRNA complementary site was amplified by PCR, sequenced and analyzed for indels by TIDE (Tracking of Indels by Decomposition). Each virus preparation exhibited transduction efficiency of >50% as assessed by imaging of mCherry expression. Analysis of sequenced DNA demonstrated indel frequency of 1040% in entire neuronal population. Overall, tested vector demonstrated high transduction efficiency and modest indel generation rate in primary neurons.

Efficiency could be increased in future by combining multiple sgRNAs. Obtained vectors are currently utilized to investigate mechanisms of protective action of PKB/Akt pathway against αsynuclein aggregation in primary neurons.

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NEUROPROTECTIVE EFFECTS OF POLYACRYLIC ACID (PAA) CONJUGATED CERIUM OXIDE AGAINST HYDROGEN PEROXIDE INDUCED CELL DAMAGE IN SH-SY5Y CELLS

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An increased oxidative stress is involved in pathogenesis of various neurodegenerative disorders including Parkinson's disease (PD). Although, cerium oxide nanoparticles are well explored in theranostics due to its antioxidant and reactive oxygen scavenging activities, the reports related to PD are scarce. Therefore, we studied biosafety and protective effects of polyacrylic acid conjugated cerium oxide (PAA-CeO) nanoparticles in human neuroblastoma SH-SY5Y cells, a cellular model for PD. PAA-CeO was synthesized by aqueous precipitation method. The Dynamic Light Scattering and Scanning Electron Microscopic images revealed spherical nature of particles with diameter about 10-20 nm and exhibited a zeta potential of -35 mV with good stability at room temperature. Different concentrations (0.5M, 0.05M and 0.03M) of PAA-CeO at different dilutions (1:1, 1:2, 1:4) were tested for cytotoxicity and 0.5M was detrimental for cells at dilutions of 1:1 and 1:2, but not 1:4. While, 0.05 and 0.03M PAA-CeO were safe in all dilutions. The cells pretreated with PAA-CeO attenuated the cell damage of SH-SY5Y cell evoked by oxidative stress inducer, hydrogen peroxide as confirmed by LDH release assay and propidium iodide staining method. These results indicate the neuroprotective potency of PAA-CeO, which should be explored in other neurotoxin-based models of PD.

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THE EFFECT OF B355252 ON NEURODEGENERATION AND NEUROINFLAMMATION IN THE MURINE MODEL OF PARKINSON'S DISEASE

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Parkinson's disease (PD) is a chronic neurodegenerative disorder mainly resulting from damage to the nigrostriatal pathway. However, an effective therapeutic approach that reverse or cure this disorder remains undiscovered. The neuropathological changes present in PD are well reflected in a murine model of PD induced by intraperitoneal administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The objective of the present study was to determine whether B355252, a phenoxythiophene sulfonamide derivative, can ameliorates neurodegenerative processes and the progress of the inflammatory reaction in the murine model of PD. Male C57Bl/10CLZD mice 10-12 month-old were used in this study. B355252 solution was administered intraperitoneally in three doses: 2,5 mg/kg, 5 mg/kg, 10 mg/kg. One day later, the mice were administered the neurotoxin MPTP (40 mg/kg), and on day 7, the animals were decapitated an the material was collected to testing. The expression of genes in the isolated brain structures was determined by real-time PCR. This study demonstrates that pretreatment with B355252 leads to dose-dependent decreasion of expression of proinflammatory cytokines IL-1α and TNF-α, which may indicate the anti-inflammatory effect of B355252. The obtained data suggest that further research on the molecule may be beneficial and may lead to the development of a new treatment option for PD.

THE EFFECT OF BLUE LIGHT ON THE PARKINSON'S DISEASE IN THE DROSOPHILA MELANOGASTER MODEL

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Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world. Still, many factors affecting its development remain undiscovered. The effect of blue light emitted by monitors, TVs and smartphones on the nervous system is a widely investigated and discussed topic in neuroscience. In fruit flies, long-term exposure to blue light has been shown

to result in reduced lifespan, motor impairment, neurodegeneration and changes in the expression levels of genes related to oxidative stress. In the present project, we focused on the effect of relatively short exposure to blue light on the exacerbation of PD. We used the park mutant strain of Drosophila melanogaster, widely used as PD model and wild-type Canton-S as control. Both strains were divided to two groups: one was exposed to blue light for 1 h, the second was kept in normal conditions. In the groups exposed to blue light changes in survival curves were observed. Changes in the expression level of genes related to the dopamine pathway, response to oxidative stress and autophagy were also demonstrated. These results show that even a brief exposure to high-energy blue light can have an effect on the organism's functioning, causing exacerbation of Parkinson's disease.

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POSTURAL CHANGES RELATED TO AGING AND PARKINSON'S DISEASE

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Aging and Parkinson´s disease (PD) are accompanied by postural instability and falls that affect daily living activities and quality of life. The balance problems and increased incidence of falls have been associated with decreased functional ability to adapt to altered sensory conditions. A sudden change of sensory input represents a transient period in balance control, which could be more demanding for vulnerable elders and PD patients. The aim was to evaluate effects of age and PD on dynamic postural responses to bilateral lower leg muscle vibration during stimulation period and immediately after the stimulation offset. Thirteen healthy young (mean age 25.0), 13 healthy elders (mean age 70.1) and 13 PD patients (mean age 63.7) were assessed by force platform and 2 accelerometers attached on upper and lower trunk. Young and elders differed during and after stimulation period, while differences between elders and PD patients were seen mainly after the stimulation offset. Analysis and clarification of postural responses in transient period may be helpful to better distinguish between changes due to age and pathological changes due to PD. On the other hand, responses to sudden changes of sensory inputs can identify people with potential fall risk regardless of age and PD.

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EFFECT OF AEROBIC-STRENGTH EXERCISE ON POSTURAL STABILITY IN PATIENTS WITH PARKINSON'S DISEASE: INTERIM ANALYSIS

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Postural instability leading to reduced mobility affects balance in Parkinson´s disease (PD). Recent studies showed that different types of interventions based on supervised physical training might result in improvement of balance-related outcomes. However, there is still lacking evidence about what type of training would be the most appropriate. In our pilot trials, we examined the postural stability of four PD patients (men, age 50-66 yrs, Hoehn-Yahr 1-2, on PD medication) before and after a 4-month combined strength-endurance supervised training, with frequency 3 × 1 h per week. Posturographic variables (amplitude/velocity of body sway, root mean square and line integral quantified from the center of pressure displacement) were evaluated during 4 static (standing on firm/foam support with eyes open/closed) and 2 dynamic conditions (vibration of lower leg muscles). Three patients showed improved postural stability manifested by smaller and slower body sway even in the most challenging sensory condition post-training compared to pre-training measurement. These results indicate that sensory feedback-based control was more effectively utilized after the intervention. The study is ongoing, and data from more patients as well as control, non-exercising group will be available for the analysis in future, to confirm the effect of regular aerobic-strength exercise on postural stability in PD patients.

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EPIDEMIOLOGICAL DATA AND CASE REPORT ON MOTONEURON DISEASE

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Motoneuron disease (MD), also known as Lou Gehrig's disease, is rare neurodegenerative disease which affects motor neurons. Patient M., 51, presented to Scientific-Practical Medical Centre of KNMU in 2019 with a 1-year history of weakness in hands with restriction

of movement in left hand and muscle twitches. Muscle weakness increased after physical strain. Over the last few weeks, his health had deteriorated. Neurological examination: Tendon reflexes on the hands, knee, achilles were increased (D>S). The muscle force in left hand – 2.5 points, on the right – 4 points and on the legs – 5 points each. Barre testis + on the left. Muscle fasciculations were present in the left forearm and neck muscles. Muscles of distal extremities were atrophied. He was ataxic in Romberg position. No other signs were identified. A needle (ENMG) showed the motor unit with signs of restructuring along neuronal type, involving the muscles of cervical, lumbar sacral thickness and bulbar group with signs of denervational process. Thus, the patient was diagnosed with MD, diffusing form with moderate upper paraparesis, bulbar disorders. He is being treated with xavron 60 mg intravenous drip N° 14 and intramuscular Neurobion 1 amp. The cause and cure of MD are topics to be researched on.

"EEGHUB.GE" DATABASE FOR STUDY EEG PATTERN IN PATIENTS WITH CNS DYSFUNCTION

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EU Project NI4OS is funded by the European Commission's Horizon 2020 program. The first online EEG database "EEGHUB.GE" in Georgia was funded and selected as a thematic service. EEG data of patients with NS dysfunction is uploaded to the European Open Science Cloud. "EEGHUB.GE" is used to study EEG characteristics in Patients with different CNS-disorder. First study revealed EEG biomarkers in 39 epileptic children aged (6-10 years) during the AED-treatment. Second study is aimed to determine the EEG pattern to hyperventilation based on time and age of patients. The presence rhythmic monomorphic theta waves of tempo-parietal region is a predicting factor for seizures recurrence. The pathological EEG reaction to hyperventilation was revealed in 985, into the 3-50 age groups. Three types of EEG reaction to hyperventilation were revealed of disorganization of the basic rhythm (than paroxysmal and epileptiform discharges) in all minutes. In the first minute was revealed ratio between all types of EEG and age, compare to second/third min. Reduction of low-frequency waves, suppression of epileptiform EEG pattern simultaneously with clinical improvement serve as biomarker. EEG-response to hyperventilation is informative for scientific and clinical study. Extension of functional test is not recommendable, especially in patients with CNS-disorders and in children.

INVESTIGATING THE EFFECTS OF PSYCHOTHERAPEUTIC IMAGERY TECHNIQUES WITH RENEWAL AND RECALL PROCEDURES

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Imagery techniques were found be effective in reducing various mental problems. There are two imagery techniques that are most commonly used for treatment: a classical imagery exposure (IE) and a more contemporary one – imagery rescripting (IR). Although it was shown clinically effective, IR is still under research in terms of neurological and psychophysiological foundations. We try to establish these foundations using a renewal and recall procedures. In our study, participants characterized by an increased fear of failure underwent a 2-weeks long imagery treatment in a between group design (IE or IR). During treatment participants were listening to the recordings of their own autobiographical events of criticism that were rescripted (IR) or presented in a prolonged way (IE). Treatment effects were assessed based on skin conductance level (SCL) that was measured both in the therapy context (recall procedure) and in the new context (i.e., in a new space; renewal procedure). Both techniques turned out to be similarly effective at recall. The results from the renewal procedure show that IR was more effective than IE, as in the new context the fear reaction reappeared in IE group.

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ORIGINAL TECHNIQUE OF SEALING CEREBROSPINAL FLUID LEAKAGE FROM DURAL SAC CAUSING SPONTANEOUS CEREBRAL HYPOTENSION

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Spontaneous intracranial hypotension (SIH) is a disease characterized by a decrease in the amount and/or pressure of cerebrospinal fluid (CSF). The cause

of the decrease in CSF is its leakage through the damaged dura. Severe, debilitating headache that occurs or worsens during verticalization is the main symptom reported by the patients which is relieved in recumbent position. Symptoms are explained by a decrease in intracranial pressure, which disrupts intracranial homeostasis. SIH treated unproperly may lead to severe and fatal complications. Most patients recover from conservative treatment, but when the patient is unresponsive to this kind of treatment the invasive methods should be performed. Right now, the golden standard for invasive SIH treatment is epidural blood patch (EBP). We present the original technique of performing the EBP injected directly to the intravertebral foramen under the CT guidance. To the addition to the procedure of EBP, we are including the postoperative care which is based on bed rest in the lateral position on the opposite side to the fistula. The method proposed by us is the effect of own clinical experience and with addition of propositions published by other authors, we believe in our method and its effectiveness in the SIH treatment.

MORPHOLOGICAL STUDY OF THE CEREBELLUM

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Changes of the cerebellar parameters may manifest as a result of multiple sclerosis, Chiari malformation, Parkinson's disease, etc. This cadaveric study was designed to investigate the variant anatomy of the cerebellum measurements and its shape. It was performed on 101 samples of cerebellum and adjacent brainstem. Cerebellar width (CW), length (CL) and height (CH) were measured according to the cranial axes. Certain methods, used to describe morphology of the cerebellum, cerebrum, liver and adrenal gland, were examined, adapted and applied to the present study. Statistical analysis revealed relative independence of the CH and its ratios. In contrast, significant correlation was found between CW and CL, as well as their ratios. The study indicates that CW and CL are the main factors of the linear relationship between cerebellar shape and age; this relationship also differs between men and women. Twenty-seven variants of the cerebellar shape were distinguished in a classification presented in this paper. It gives distinct description of the cerebellar shape relatively to all three dimensions. These results may be valuable for further morphological investigations of the cerebellum and for the MRI diagnostics.

FRACTAL DIMENSION AS A MEASURE OF ATROPHIC CHANGES IN HUMAN CEREBELLUM THROUGHOUT ADULTHOOD

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Distinguishing between morphological changes in cerebellar structures while normal aging and pathological ones by various diseases is especially important for clinical practice. In our study we aimed to characterize atrophic changes in cerebellum while normal aging. The present study included investigation of macrophotographs of 100 midsagittal sections of cadaveric cerebella obtained from patients whose death was not tied with brain pathology (age range 20-95 years) and T2-weighted MRI scans of 120 apparently healthy individuals (age range 18-86 years). We employed fractal analysis using conventional box counting method to measure fractal dimension (FD) of white matter in cadaveric cerebella and original, author-modified pixel dilating method to measure FD of outer linear contour of cerebellar cortex on MRI scans. The average FD value of cerebellar white matter, measured in cadaveric specimens, was 1.37±0.01; the average FD value of cerebellar cortex contour, measured on MRI scans, was 1.40±0.01. We revealed significant negative correlation relationships between determined FD values and age ($r=-0.92$, $P<0.05$, and $r=-0.53$, $P<0.05$, respectively). Thus, the FD values of cerebellar white matter and outer linear contour of cerebellar cortex decrease significantly with age. Fractal analysis can be used to characterize atrophic changes both in normal aging and by various pathologies.

ON THE TRAIL OF SOMNAMBULISM

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Somnambulism, commonly known as sleepwalking, affects only 3% of the adult population. It is a parasomnia associated with the NREM phase characterized by incomplete awakening during sleep, with simple or complex behaviors with simultaneous full or partial amnesia of nocturnal experiences. Based on self-report and statistical analysis in SPSS of the results from the questionnaires, we investigated the effects of evening chronotype, COVID-19 pandemic (SARS-CoV-2) and sleep disorders on the occurrence and frequency of sleepwalking episodes in adults. No significant statistical differences were found between the incidence and frequency of sleepwalking episodes and the mentioned factors. However, this does not exclude their influence. The

conducted study is a good start for a rarely studied group of adult sleepwalkers. Future work should focus on increasing the study group and expanding the research methodology.

REPRODUCIBILITY OF SPATIAL SUMMATION OF PAIN EFFECT DURING COVID-19 PANDEMIC

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The ongoing COVID-19 pandemic brings with it many restrictions which also affect the conduct of research. The purpose of the study was to replicate spatial summation of pain (SSp) effect using the adaptation of laboratory procedures using non-laboratory commercial equipment. Cold pressor task was used to induce SSp effect by immersing the hand in the cold water (5°C). Healthy participants (N=68) immersed their non-dominant hands (divided into 5 segments) in the cold water. Two conditions were used gradual immersion of the hand (Ascending) and gradual withdrawal of the hand (Descending). Pain intensity was measured on visual analogue scale, ranging from 0 (no pain) to 100 (the most intense pain imaginable). In the study influence of psychological factors such as volunteer's expectations of pain intensity on the perception of pain were also compared. Results showed significant effect of: the factor "area" on perceived pain intensity ($\chi w(4)=116.9$, $p<0.001$), thus SSp effect was reproduced, the factor "time" of measurement ($\chi w(2)=157.5$, $p<0.001$), indicating that sensitization enhanced summation. Moreover, there were significant correlations between expectations and experienced pain, which indicate that pain expectations predict pain in a SSp paradigm.

NEURONAL UNDERPINNINGS OF LANGUAGE PROCESSING DURING LIPREADING – FMRI STUDY

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Lipreading is an ability that helps understand speech in noisy conditions. It can enable people with hearing impairment to improve speech perception. This ability includes processing of visemes, getting to auditory representations and then analyzing lexical meaning. Studies on correlates of lipreading show various areas as relevant to this skill. These differences may stem from differing cognitive paradigms used. Our goal was to investigate aspects of language processing during lipreading in a robust manner. We examined 43 right-handed subjects using lipreading task during the fMRI. For the task we used 20s clips of actor speaking about various topics. Clips where: with sound; without sound; backwards, static face without sound. In half of the blocks, full sentences were presented while in other half only words (nouns). To assess the effects of factors, rmANOVA was conducted. The analysis of lexical *vs.* non-lexical factor showed numerous language-related regions (e.g., STG, MTG, and TP). Words *vs.* sentences factor yielded two clusters in the left p+mTP as well as pSTG. Results of these analyses elucidate similarities and differences in patterns of activity during lipreading. While bulk of our results overlaps with regions previously implicated in literature, we identified additional patterns of task-specific activity.

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NEURAL CORRELATES OF THE SEMANTIC AND PHONOLOGICAL VERBAL FLUENCY TASK

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Verbal fluency is a task widely used in research on cognitive control and language processing. It occurs in two versions. In both participants are asked to produce as many words as possible pertaining to a given semantic category (semantic fluency) or starting with a given letter (phonological fluency). Typically, studies on verbal fluency are limited to a small number of categories or letters. This study extends previous findings by using more cues and it explores the brain basis of mechanisms engaged in the verbal fluency task. Forty-one participants performed a semantic and phonological fluency task during the fMRI scanning. On a behavioral level we found that the participants produced more words in the semantic fluency task compared to the phonological variant. On a neural level, both verbal fluency tasks were linked to

significant activations in a network of left-lateralized structures including the middle frontal gyrus, inferior frontal gyrus, paracingulate gyrus, and fusiform cortex. These structures were previously shown to be important nodes for language processing as well as cognitive control. Preliminary analyses also indicate differences between semantic and phonological variants. As such, our study confirms that verbal fluency is a task that engages both language-related but also cognitive control resources.

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HAPPY JUST NOW OR HAPPY ALWAYS? ERP CORRELATES OF STATE AND TRAIT ADJECTIVE PROCESSING

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Adjectives denoting affective experiences can be grouped into words that describe stable traits (personality, e.g., "honest") or transcient states (moods, e.g., "tired") or indeed, both (e.g., "active"). The latter type of adjectives were the focus of the study, in which the semantic context was manipulated in order to induce the same adjective's processing as either a state or a trait word. The pertinent question was what would be the first processing stage, as evidenced by the ERPs, to be modulated by differences in meaning encoding related to the affective (state or trait) experience. Thirty-three adjectives were chosen form Polish normalised dataset and each completed the sentence, which pointed to state or trait interpretation of the final (target) word. Sixty-four channel EEG system was used for recording. The study found significant modulation in P150 time window with larger amplitudes of the component in response to the encoding of an adjective as a trait word in comparison to the state interpretation. The study pointed then to the possibility that the word's meaning qualified by affective context related to specific experience was analysed within the first 200 ms after target stimuli onset.

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UNDERSTANDING BRAIN REORGANISATION DYNAMICS DURING LEARNING TO READ BRAILLE: (DIS)SIMILARITIES BETWEEN TACTILE AND VISUAL READING

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It is well established that the human brain is subject to reorganisation upon learning new skills. Previous studies on sighted individuals showed enhanced brain activity when reading using touch. After three months of tactile Braille reading, it was visible in motor and language areas, including the visual word form area (VWFA). However, there are still open questions about the time-course of neuroplasticity in the first weeks of learning. Seventeen participants (female, aged 19 – 23) underwent a seven-month tactile Braille course with elements of visual Braille. We tested Braille's letter and word reading speed in tactile and visual domains and observed a positive trend throughout the course. Lexical Decision Tasks (LDT) in tactile and visual Braille were used in fMRI. After just 7 days of learning, we observed changes in activation in the reading network (including VWFA) in visual LDT but not in tactile LDT, which produced VWFA activation only after 6 weeks of learning. The results suggest unimodal plasticity precedes cross-modal plasticity, while the latter occurs quicker than previously thought. We also mapped similarities and differences in activation during LDT tasks. We observed similarities in regions of the reading network and differences mostly in occipital areas and motor cortex.

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THE PREFRONTAL CORTEX UNDERPINNINGS OF HOW COGNITIVE LOAD REDUCES DIETARY SELF-CONTROL: AN FMRI EXPERIMENT

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Previous experiments have shown poorer dietary self-control under cognitive load. Neuroimaging studies on food-related decision making revealed increased activity in dorsolateral prefrontal cortex (dlPFC) in dietary self-control, the integration of health and taste values in ventromedial prefrontal cortex (vmPFC), and the dlPFC support for health values incorporation in the vmPFC value signals. We expected that increased cognitive load during food choices reduces both choice-related dlPFC activity and the link between health value and vmPFC activity, resulting in impaired dietary self-control. Thirty-six participants rated the healthiness and tastiness of foods. In the fMRI scanner they made 90 food choices, including 60 self-control challenges (healthier *versus* tastier foods). Choices were made twice: after memorizing seven-digit and one-digit numbers (cognitive load manipulation). Choice-related brain activity was analyzed while controlling for load-specific activity. dlPFC activity was lower in high compared to low load across all decisions, irrespective of self-control challenge. The choice healthiness (chosen – unchosen foods rating) correlation with vmPFC activity was weaker under high load. Increased cognitive load might reduce self-control by shifting dlPFC resources from choice-related to load-specific activities. We found no behavioral effect of memory load on self-control in food choice, possibly due to noisier decisions under load (our ongoing analyses).

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WOMEN'S BUT NOT MEN'S ABILITY TO IDENTIFY THE TWO-DIMENSIONAL CROSS SECTION OF A 3D OBJECTS IS RELATED TO SOCIAL AND EMOTIONAL FACTORS

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Sex and sex hormones influence spatial abilities. However, the effect of hormonal contraceptives is underinvestigated. Spatial cognition is also influenced by socio-cultural factors and individual differences. We aimed to evaluate the influence of biological, non-biological factors and interaction between them on spatial abilities assessed using Cross Section Task (CST). 33 men and 117 women participated in the study. Women were divided into: oral contraceptives users (OC, n=26), intrauterine device users (IUD, n=31), naturally cycling women in follicular phase (NCF, n=35) and in mid-luteal phase (NCL, n=25). Participants performed paper-pencil CST and completed questionnaires assessing demographic information, masculinity and femininity, fatigue, emotional arousal, etc. Men outperformed NC women and OC, but not IUD users. Multiple regression analysis was performed to predict performance based on demographic, hormonal status, masculinity, femininity score, and emotional arousal for women and men separately. Interestingly, the regression models revealed significant predictors for women, but not men. Women's performance was negatively related to emotional arousal, but positively to occupation in STEM field and masculinity score. Overall, study results suggest that men, regardless of individual characteristics, perform CST task better than women. Whereas different biological and social factors affect women's performance.

TRACING THE BRAIN REWARD SYSTEM'S RESPONSE TO "WITTY DESIGN"

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Witty design has been described by graphic design theorists as 'a smile in the mind'. In general, this means an intelligent and attractive idea embodied in graphics, but one can discover the same qualities in industrial design, architecture and even street art. At the subjective level, we love witty design because it appeals to intelligence and sense of community with the author. Considering cognitive process theories, one may assume links with the balance of familiarity-surprise, humour, aesthetics, closure, and 'the joy of communication'. An exciting research challenge is to explore the neural basis of such an intellectual pleasure, hypothesising activations typical for aesthetic experience, amusement or surprise. In a preliminary investigation we used 40 examples of good and poor logos and 40 various expressions of street art (mainly graffiti). Six young, healthy volunteers assessed how much did they like pictures on a 5-point scale, during MRI registration. Seventeen neural networks were identified with ICA. Apart of quite obvious activations in visual and motor networks, the DMN and DAN interplay was visible. Differences of time courses for pleasant and neutral stimuli were observed in mPFC, anterior insula and caudate nucleus. Both types of 'intelligent' stimuli (logos, street art) activated the same regions.

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THE SAME OR NOT THE SAME? ELECTROPHYSIOLOGICAL MARKERS OF EXTERNAL AND INTERNAL SPATIAL ATTENTION IN SIMPLE TWO-ELEMENT DISPLAYS

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External spatial attention refers to the selection of currently present information in the environment while internal spatial attention refers to the selection of stored information that may be held active in short-term memory. An important question is whether these two types of selection involve the same neural mechanisms. Earlier studies with multi-element displays support this view, but no study was yet able to show support with simple two-element displays, probably because of alternatively employed task strategies. An EEG experiment was carried out with a modified version of a cued spatial selection task. Two out of four possible shapes were presented simultaneously in the left and right visual fields. A color cue indicated which shape was the target. Participants had to indicate the identity of the target by a manual choice response. The cue appeared either before or several seconds after shape onset (i.e., a pre- or a post-cue), which implies either external or internal selection. Time-frequency analyses revealed that the act of selecting relevant information was associated with a contralateral reduction of alpha power over visual areas in both cue conditions. These results provide further support for the view that internal and external selection involve the same neural mechanism.

3D MENTAL ROTATION: LINKS BETWEEN TASK PERFORMANCE, EYE MOVEMENTS AND SEX HORMONES

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It is observed that mental rotation tasks are performed better by men than women and that the performance of such tasks is related to sex hormones. Additional information regarding cognitive processes during mental rotation and their relationship with sex and/or the status of sex hormones could be gathered using eye-tracking. The aim of this study was to evaluate the parameters of eye movements during mental rotation task and their links with task performance, sex, and sex hormones.

The performance of 89 participants (33 men, 33 naturally cycling women, and 23 hormonal contraceptives users) was evaluated while their eye movements were tracked using EyeLink 1000. Saliva testosterone and progesterone concentrations were measured to estimate links between sex hormones and task performance or parameters of eye movements. The mental rotation task was performed better by men than naturally cycling women. To decide if two simultaneously visible objects are identical, all participants, regardless the group, made mental manipulations while looking at the rotated object. For men, testosterone positively correlated to the total duration of fixations at the first observed figure before looking to another one. Progesterone was related to faster responses in naturally cycling women and to higher accuracy in oral contraceptives users.

HOW EMOTION INFLUENCES MEMORY OF EVENTS IN SPACE AND TIME?

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Our daily lives consist of a continuous stream of experience, yet our memories of past experiences are organized into distinct events, like chapters in a book. Given that we cannot remember everything we experience, we need our memory system to flexibly determine which events will be stored for future use. In particular, remembering events that are emotional is critical to our survival. Indeed, our memories of such events are particularly strong, vivid, and later remembered with high confidence. However, existing evidence is less homogenous when it comes to memory for their context, such as the where and when an event happened. Here, we addressed these critical gaps using an innovative approach, by combining behavioral and physiological measures with a novel memory paradigm in virtual reality (VR). This approach allowed us to investigate how emotion affect our ability to segment experience into events, based on the shared or distinct context in space and time. Our participants better remembered temporal order of objects coming from the same *vs.* different events. However, this 'event segmentation' effect dif-

fered between emotional or neutral events. The present results suggest that emotion affects the way we organize our memories of events in space and time.

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AN ERP STUDY OF VISUAL WORKING MEMORY: NO INFLUENCE OF SEX, SEX HORMONES AND HORMONAL CONTRACEPTIVES

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Despite accumulating evidence of the influence of sex hormones on cognitive function, research on the effect of sex hormones on visual working memory (VWM) is controversial and limited. This study aimed to investigate the influence of sex and female hormonal status (phase of menstrual cycle, use of hormonal contraceptives) on VWM performance and electrophysiological measures. Men (n=30), naturally cycling women in the follicular phase (n=30) and luteal phase (n=36), and hormonal contraceptives users (n=34) performed a bilateral VWM change detection task while their ERPs were recorded. The effects of group and experimental conditions on behavioral (response time, performance and capacity) and electrophysiological (contralateral delay activity (CDA)) measures were assessed. Behavioral measures of VWM and average CDA amplitude did not differ significantly between groups and did not correlate with sex hormone (estradiol, progesterone, and testosterone) levels. The results suggest that VWM is not influenced by sex and sex hormones, women's menstrual cycle phase, or use of hormonal contraceptives.

DIFFERENT MOTOR CONTROL INVOLVEMENT IN PERSEVERATION AND LEARNED IRRELEVANCE

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In visual discrimination learning, reward contingency changes in categorisation tasks affect individual performance, which is tied to costs of attention shifting. Two recently described mechanisms of perseveration (PE) and learned irrelevance (LI) underlie this phenomenon. A newly developed LI/PE task was performed in young, healthy adults to understand temporal dynamics of motor control through combination with EMG recording. The task perfectly differentiated LI and PE conditions. RTs were significantly longer, and error rate was higher in PE, as compared with LI. Both set-shifting conditions differed from the control condition in longer RTs and decreased accuracy. EMG recording revealed an increased number of subliminal erroneous response activations in both attentional set-shifting conditions when comparing with the control condition; the efficiency of inhibiting these subliminal erroneous response activations was decreased in PE as compared with the LI condition, and similarly for both attentional set-shifting conditions as compared with the control condition, and there was the increased duration of premotor times (intervals between stimulus onset and related muscular response) in both attentional set-shifting conditions compared to the control. These results suggest that motor control processes differ across PE and LI conditions.

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INTRAVOXEL INCOHERENT MOTION EXPERIMENT PLANNING

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Intravoxel incoherent motion (IVIM) is a specific application of diffusion-weighted imaging (DWI) in magnetic resonance imaging (MRI). The IVIM concept has been proposed to estimate perfusion in tissues, as blood flow is similar to a pseudo-diffusion process. Despite IVIM popularity, there is no easily accessible software allowing IVIM parameters calculation and analysis, nor is there a unique golden standard proposed for performing IVIM experiments, especially in low perfused tissues such as brain. In this work, a toolbox allowing IVIM-MRI parameters calculation (using three basic methods: using trust-region single step fitting, trust-region segmented fitting, and segmented grid search), visualization, and synthetic signal generation, is presented. The app was realized in MATLAB environment using AppDesigner for user-friendly GUI and Curve Fitting Tool functionalities for the fitting algorithm. An experiment, parameters calculation of synthetically generated IVIM data derived from different b-values and various SNR levels, was performed and results described. Example *in vivo* dataset was segmented according to AAL and IVIM parameters were calculated.

UNLOCKING THE MUSICAL BRAIN: AN ECOLOGICAL APPROACH TO PLAYING THE PIANO IN AN MRI SCANNER

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The piano is a popular instrument in musical practice, but only a few MRI studies investigate the neuronal mechanisms underlying playing it. MRI-compatible piano requires adaptations for size and materials used. Moreover, study designs often sacrifice ecological validity for experimental controllabillity. We present open-source, proof-of-concept experimental fMRI paradigms used for the validation of our original, highly ecological, MRI-compatible keyboard. Twenty pianists (female, 19-26 yo) first listened to familiar naturalistic polyphonic musical stimuli, and then replayed them. Neuroimaging data were preprocessed with fMRIPrep and statistically analysed in SPM12. We directly compared listen and playback conditions using one-sample t-tests and cluster-correction. Neuroimaging data analyses revealed stronger bilateral activation related to listening in precuneus, superior and middle temporal gyri, medial frontal cortex, angular and supramarginal gyri, hippocampus, thalamus, putamen, caudate nuclei, supplementary motor cortex, middle frontal gyrus and cerebellum. In the literature, these regions are associated with musical processing, memory and familiarity, and motor planning. In contrast, playback evoked stronger responses in the left sensorimotor area, right cerebellum and bilateral operculum, which are involved in motor control and performance monitoring. We show that naturalistic, ecological MRI study on piano playing is feasible and provide off-the-shelf solutions to facilitate open and replicable science.

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EFFECT OF MUSICAL TRAINING ON RHYTHM PERCEPTION – FMRI ANALYSIS

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Previous research shows that musicians, with years of musical expertise, may have a different neural pattern of rhythm perception than non-musicians. We tried to answer if this can be also observed in children following shorter musical training. 26 children with previous musical training lasting a minimum of 2 months and 26 children without this experience listened to pairs of rhythmic patterns in an fMRI scanner and had to decide if the two rhythms are the same or different. Groups did not differ in task accuracy. Even though we didn't find an effect of short-term musical training on the neural pattern of rhythm perception, we observed a tendency in contrast between listening to the pairs of the same and different rhythms. Children after musical training showed increased activation in left postcentral gyrus / superior parietal gyrus (vox. = 574) and left paracentral lobule / supplementary motor area (vox. = 500) compared to control group (p < 0.005 (unc.)). It can come from an attempt to repeat the rhythm pattern while listening to the same rhythms by children after musical training. Overall, the results didn't prove that differences in the neural pattern of rhythm perception can be observed even in children following short musical training.

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CAFFEINE – EFFECT ON SHORT-TERM MEMORY AND CONCENTRATION

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Caffeine is the most popular central nervous system stimulant in the world. The aim of the study was to test its effect on short-term memory and concentration. The experiment involved 30 volunteers aged 20 to 45 who underwent a Rey test after consuming a drink with or without caffeine. The test consists in remembering fifteen words from a previously prepared list, and then repeating them after thirty min. The allocation to the research group – with caffeine or the control group – without caffeine was determined by the results of a previously conducted survey, which took into account the phenomenon of pharmacological tolerance. The results obtained after conducting the study confirm our thesis on the influence of caffeine on working memory and concentration. It turns out that people exposed to caffeine obtained much higher results in Rey's test compared to people who were not exposed to the effects of caffeine.

CORTICAL SOURCES OF ELECTRICAL ACTIVITY, RELATED TO THE CESSATION OF A PREPARED MOTOR REACTION IN HUMANS

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Active inhibition is responsible, to a significant extent, for the voluntary cessation of the prepared motor phenomenon in humans. To study such inhibition the Stop-Signal paradigm is frequently used.

This work aims to detect the cortical sources of localization of event-related potentials while inhibition of an initiated motor program.

A total of 35 men and 40 women, healthy, and right-handed, participated in the study. According to the Stop-Signal task paradigm, each participant when receiving the presented Stop signal, stopped the initiated reaction to the Go stimulus. EEG recordings were analyzed in the frontal, central, and parietal lobes of the cortex. Data was processed with the method of low-resolution electromagnetic tomography – LORETA (the sLORETA software).

The cortical sources of the event-related potentials under the experimental conditions were consistently localized in the posterior cingulate cortex (Brodmann area 30) and the middle frontal gyrus (Brodmann area 6) mainly in the right hemisphere in women, whereas in men – in the left hemisphere superior (Brodmann area 38) and middle (Brodmann area 21) temporal gyri, respectively.

POSTER SESSION 3

NEUROLIGIN-2 IS CRUCIAL FOR LONG-TERM PLASTICITY OF GABAERGIC SYNAPSES

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Only recently, researchers have begun to explore complex molecular mechanisms of long-term plasticity at inhibitory GABAergic synapses. Although, an extensive analysis has been carried out, very little is known about the involvement of adhesion proteins and the input specificity of GABAergic plasticity. Therefore, this study aimed to investigate the role of trans-synaptic interaction between neurexin and neuroligin-2 in inhibitory synaptic plasticity at different GABAergic synapses in CA1 hippocampus. We recorded mIPSCs or optogenetically evoked PV-IPSC, and SST-IPSC in CA1 pyramidal neurons and induced iLTP using a short-term application of NMDA. Additionally, we used neurolide-2, a peptide that blocks the interaction between neuroligin-2 and neurexins. We showed that bath application of neurolide-2 abolished NMDA-iLTP of mIPSC (ctrl: 118±5%, neurolide-2: 92±2%; $p<0.001$). Furthermore, the interaction between neuroligin-2 and neurexin shapes iLTP only during the early phase of plasticity induction. Moreover, interference in the adhesion of neurexin-neuroligin-2 during iLTP blocked also the increase in the area of synaptic gephyrin clusters and decreased synaptic clusters of neuroligin-2. Interestingly, neuroligin-2 controls both SST-iLTP (ctrl: 115±9%, neurolide-2: 89±7%; $p<0.05$) and PV-iLTD (ctrl: 88±4%, neurolide-2: 106±8%; $p<0.05$). Taken together, these results characterize neuroligin-2 as a crucial facilitator of plastic changes at different GABAergic synapses.

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HABITUATION FOR ANNTENAL STIMULATION OF MADAGASCAR HISSING COCKROACH

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Neural stimulation can be employed to create cyborg insects. Their locomotion could be modified by applying a specific electrical stimulus. Several species from Blattodea order (cockraoches) possess enough strength to carry an electric circuit while retaining relatively small size allowing them to enter places inaccessible to humans. Therefore, their use can be beneficial for many tasks. For example, in rescue operations during natural disasters. They could collect data on victims trapped under the rubble. Simultaneously their usage is more cost-effective than the production of small robots. However, one of the many challenges in constructing such biobots is the habituation to driving stimuli after a relatively short period. The presented poster describes research conducted on Madagascar hissing cockroaches (*Gromphadorina portentosa*) on habituation to electric stimuli. In the study, the 500 ms square wave pulses with a 1 V amplitude and a frequency of 55 Hz in applied cyclically every three seconds were used. The pulses were delivered to exposed antennal nerves by a custom-built stimulator developed using the Arduino platform. Responses indicated by

changes in the direction of locomotion in an arena were recorded and the insects' movements were tracked using the DeepLabCut markerless tracking framework and analyzed in R using trajr package.

TRAIT DIFFERENCES IN SENSITIVITY TO NF ARE ASSOCIATED WITH EXPRESSION OF GENES RELATED TO SEROTONERGIC NEUROTRANSMISSION

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Aberrant sensitivity to negative feedback (NF) has been proposed to be an important factor in the development and maintenance of depression. Because both; sensitivity to feedback and depressive disorder are associated with changes in serotonergic neurotransmission, the present study was devoted to the investigation of differences in the expression of genes associated with this neurotransmitter, between rats displaying trait sensitivity/insensitivity to NF (NFS/NFI respectively).

The rats were tested in a series of 10 probabilistic reversal learning tests, which allowed us to classify each animal as trait NFS or NFI. Subsequently, using RT-qPCR, we evaluated the differences in the mRNA level of genes encoding serotonin receptors in the dorsal (dHip) and ventral hippocampus (vHip) between the rats displaying NFS and NFI traits. The results were further validated, at the protein level, using ELISA.

Trait NFS was associated with a higher Htr2a expression in the vHip, and a lower Htr7 expression in the dHip as compared to NFI.

Trait differences in sensitivity to NF are associated with expression of genes related to serotonergic neurotransmission.

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EFFECTS OF PRAZOSIN AND PROPRANOLOL ON THE SURFACE CHARGE AND ENZYME ACTIVITY OF RAT BRAIN DURING DIFFERENT STAGES OF SLEEP

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Sleep and wakefulness are behavioral and physiological activities. Sleep has been defined as a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment. It is modified form of the basic rest activity cycle. We have studied the effect of Norepinepherine, Serotonin (5HT) individually, in combination and in presence of receptor antagonists Prazosin and Propranolol in different permutations and combinations on the surface charge and enzyme activity of rat brain synaptosome using biochemical tests, microelectrophoresis and precision light scattering techniques. It was found that Norepinepherine increases enzyme activity. It was also validated that NE induced increase is blocked by prazosin which is a α-1 adrenoceptor blocker antagonist but propranolol which is a β adrenoceptor blocker antagonist cannot block it. There is a marginal but significant increase in enzyme activity. Propranolol seems to block 5HT mediated increase in enzyme activity. When both NE and 5HT are given in combination an increase in enzyme activity has been found which is equal to the sum of the two given separately. Both Prazosin and Propranolol could decrease the basal values of the enzyme which could be due to some mechanism involving endogenous NE and 5HT present in the sample or by other mechanism leading to nonspecific binding and decrease of ATPase activity. The results seem to assume significance of surface charge and enzyme activity in response to the REM and non REM stages of sleep. Many sleep disorders could be addressed by studying the significance of NE and 5HT with blockers.

THE ROLE OF THE HIPPOCAMPUS IN SENSORY PRECONDITIONING TASK IN A MOUSE MODEL

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Our daily choices are often triggered by stimuli that have not been explicitly associated with a reinforcer. This process is called higher-order conditioning (also known as mediated learning) and can be assessed by sensory preconditioning. This task involves repeated simultaneous presentations of two low-salience stimuli (e.g., light and tone) and a devaluation phase where one of these stimuli is paired with an unconditioned stimulus (e.g., foot-shock). The result is a conditioned response (e.g., freezing response) to both the conditioned (direct) and the non-conditioned (mediated) stimuli. In our study, male and female mice underwent a protocol of sensory preconditioning. During preconditioning, mice were ex-

posed to simultaneous presentation of light and tone. In conditioning, the light was devaluated by pairing a mild foot-shock. Finally, the animals performed two tests where mice were exposed to tone (mediated) and light (direct) in a different context to avoid fear elicited by the context. Our results indicated that female mice exhibited a higher percentage of freezing in the presence of mediated cue than males. Importantly, we also uncovered that light-tone sensory preconditioning could be a hippocampal-dependent task. Overall, we implemented a new mouse sensory preconditioning protocol, we suggest that it is hippocampal-dependent and, we observed a sex-dependent behavioral effect.

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SPATIAL PHARMACOTRANSCRIPTOMICS: THE EFFECTS OF ANTIPSYCHOTIC DRUGS ON GENE EXPRESSION IN THE MOUSE FOREBRAIN

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Psychotropic drugs induce complex patterns of cell-type specific gene expression, which enable long-term effects on neuronal activity. We hypothesized that the discrete patterns of gene expression correlate with the efficacy and adverse effects of the treatment, and thus that drug-induced transcription could be used as a predictor of the properties of novel drug candidates. 10xGenomics Visium Spatial Gene Expression technique was applied to comprehensively map changes in gene expression induced by a single administration of clozapine (0.5 mg/kg) or risperidone (0.5 mg/kg) in the prefrontal cortex and striatum of C57BL/6 mice. Using the Visium system we have performed RNAseq on coronal brain sections. The alignment of reads to the reference genome mm10 (GRCm38; „2020-A") was performed using a custom analysis method that assessed read distribution and assigned reads to genes based on sequence proximity. So far we find that unsupervised clustering of the sequencing results correctly recapitulates known neuroanatomical features in the region and find expected drug-induced changes. Further work is aimed at identifying statistically significant spatial differences in drug-induced gene expression with spatial resolution.

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EVALUATION OF THE NEUROCOGNITIVE EFFECTS OF KETAMINE IN AN ANIMAL MODEL OF DEPRESSIVE DISORDER

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Depression is a mental disorder of global concern and it is caused due to psychological stress. Ketamine is an N-Methyl D-Aspartate (NMDA) receptor antagonist, reviewed to have potential as a neurocognitive drug. This study is aimed to assess the antidepressant potential of ketamine by evaluating neuro-behavioral changes relative to neurocognition. The forced swim test (FST) induced model of depression was adopted. 20 mg/kg (IV) ketamine and 20 mg/kg oral fluoxetine were given. Thirty adult Wistar rats used were divided into six groups (n=5): A= Control, B= FST, C= ketamine, D= fluoxetine, E= FST + ketamine and F= FST + fluoxetine. The excised brain tissues were fixed in 4% paraformaldehyde, and prefrontal-cerebellar cortices were processed and stained. The treatment was for three days. Statistical significance was set at ($p<0.05$) using the Tukey *post-hoc* test. Ketamine-treated FST group had a significantly improved anhedonia, reduced immobility time, and improved motor function when compared to the FST group at $p<0.05$. The neuropathology of the prefrontal-cerebellar cortex of the FST group was characterized by neurodegeneration, proliferation of reactive astrocytes, and decline in synaptophysin expression which was averted by ketamine treatment shown by a decline in reactive astrocytes and improved synaptophysin expression that results in the improved anhedonia and decline in immobility time. Ketamine can be a neurocognitive drug acting on the neuron-astrocyte to reverse neuroinflammation and increased synaptogenesis in the prefrontal-cerebellar cortex.

INVESTIGATION OF THE MOLECULAR MECHANISM OF ANTIDEPRESSANT-LIKE ACTION OF KETAMINE AND 5-HT6 RECEPTOR AGONIST (ST1936) IN MALE RAT CEREBELLUM

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Depression presents several limitations in current treatment. Scientists investigate the mechanisms of action of antidepressants and search for new, more potent drugs. Neuroimaging techniques indicate that the cerebellum plays a role in depression pathophysiology. The cerebellum is not only involved in motor functions but also in plasticity. It alludes to emotional-cognitive difficulties with the cerebellar cognitive affective syndrome. Our previous studies showed that ST1936, the 5-HT6 receptor agonist, and ketamine were active in the negative version of the affective bias test (ABT). Moreover, behavioral effects were accompanied by molecular changes in the hippocampus and mPFC. In this study, we aimed to evaluate the molecular antidepressant-like activity of ST1936 and ketamine in the rat cerebellum concerning the changes observed in ABT. The ST1936 and ketamine effects on AKT, mTOR and ERK1/2 phosphorylation have been examined *ex vivo* with AlphaLISA SureFire technique. We observed a decreased level of p-ERK1/2 in the rat cerebellum after a single ST1936 but not ketamine administration. In the cerebellum of rats, neither ST1936 nor ketamine influenced phosphorylation of AKT and mTOR.

Decreased phosphorylation of ERK1/2 in rat cerebellum might be related to the mechanism of the antidepressant-like action of ST1936.

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INFLUENCE OF A2A TREATMENT ON DEPRESSIVE-LIKE BEHAVIOR AND D2-RECEPTOR AVAILABILITY IN RATS EXPOSED TO REPEATED SOCIAL DEFEAT

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The interaction between the dopaminergic and adenosinergic systems in depressive phenotypes remains largely unexplored. This study aimed to investigate the effect of adenosine A2a receptor modulation on the development of depressive-like behavior and dopamine D2 receptor availability, in rats exposed to repeated social defeat. Thirty-eight rats were divided into three groups which received vehicle, the A2A agonist CGS21680 (0.1 mg/kg), or the A2A antagonist KW6002 (1 mg/kg). Rats underwent 5 days of repeated social defeat using the resident intruder paradigm. Anhedonia-like and anxiety-like behavior were assessed using a sucrose preference and open field tests respectively to validate the depressive-like phenotype. D2 receptor availability in the striatal regions was assessed using [11C]raclopride-PET. Treatment with both CGS21680 and KW6002 prevented a decrease in sucrose preference and decreased locomotor activity after social defeat. Both drugs decreased D2 receptor availability in the striatum, in particular in caudate-putamen. A2AR-antagonist treatment also decreased it D2 receptor availability in the nucleus-accumbens. Our study showed that the treatment with either an A2AR agonist or an A2AR antagonist prevented the development of depressive-like behavior, and reduced the availability of D2R in the striatum after exposure to RSD.

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FROM OUT-GROUP RESERVE TO IN-GROUP FAMILIARITY – LESSONS FROM MICE HOUSED UNDER SEMI-NATURALISTIC CONDITIONS

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In social species, diverse attitudes toward in-group and out-group individuals are reflected in the well-conserved neuronal background. Understanding those brain mechanisms may be facilitated by the behavioral protocols allowing to elicit naturalistic social behavior. To investigate the emergence of social bonds between two unfamiliar groups, we used mice, a species of highly social nature. Each of the groups came from a different colony. Animals were tested in Eco-HAB, a computer-controlled system mimicking natural murine habitats. The Eco-HAB territory was divided into two equivalent parts – one for each group – which were subsequently merged. From that moment the animals from both groups could freely interact. We show that immediately after the merger animals prefer spending time and following in-group conspecifics rather than the alien ones. However, to a varying degree, depending on both, the particular group and the individual. In the following hours, the social structure starts shifting, with some mice sticking to their previous social preferences while others form close relationships with strangers.

In summary, we present the data illustrating the process of consolidation of the two previously unfamiliar groups. The presented discoveries form a foundation for further studies of the brain mechanisms underlying novel social bonds.

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TRAIT DIFFERENCES IN SENSITIVITY TO NEGATIVE FEEDBACK DO NOT INTERACT WITH THE EFFECTS OF ACUTE TREATMENT WITH AGOMELATINE ON BEHAVIOR OF RATS IN THE FORCED SWIM TEST

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Depression is one of the biggest threats to modern society. It has been postulated that certain cognitive traits may influence the development, progression as well as treatment of this disorder. One of these traits is sensitivity to negative feedback (NF). The present study was designed to examine if trait sensitivity to NF could alter the effects of antidepressant agomelatine measured in the forced swimming test (FST) in rats. The rats were tested in a series of 10 probabilistic reversal learning tests, which allowed us to classify each animal as trait sensitive/insensitive to NF. Subsequently, we evaluated the effects of a single administration of 3 different doses of agomelatine (5, 10, and 40 mg/kg) on behavioral despair and other behaviors measured in the FST. We observed no statistically significant interaction between trait sensitivity to NF and the effects of acute agomelatine treatment on immobility, climbing, and swimming behaviors measured in the FST. Trait differences in sensitivity to NF do not interact with the effects of acute treatment with agomelatine on the behavior of rats in the FST.

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THE EFFECTS OF SIMULTANEOUS INHIBITION OF SERT AND THE 5-HT6 RECEPTOR ON COGNITIVE FLEXIBILITY OF MALE RATS

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The ascending serotonergic system modulates a plethora of cognitive and affective functions in humans and animals. Dysfunctions of this system are implicated in both psychiatric and neurodegenerative disorders, with cognitive inflexibility being a common symptom for both. Here, we tested the impact of two novel dual-action compounds that inhibit the serotonin transporter (SERT) and the 5-HT6 receptor, on the ability to adjust behavior to environmental changes. By combining two forms of activity, such drugs should be less prone to side-effects. Three groups of male Wistar rats were evaluated in the Attentional Set-Shifting Task (ASST) under either vehicle- or drug-treatment (MM393, 7.5 mg/kg; MM394, 2.5 mg/kg), in the active/dark phase of the diurnal cycle. The ASST probes two forms of cognitive flexibility i.e., reversal learning and set-shifting, that are contingent on orbitofrontal and medial prefrontal cortex, respectively. Following acute treatment with MM394, >60% of rats did not complete all of the 7 stages of the ASST. Compared to vehicle, MM393 had no effect on cognitive flexibility and caused a significant increase in rats' latencies to make a choice. Simultaneous inhibition of SERT and 5-HT6 might impact motivation to perform complex decision-making tasks.

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PRECLINICAL INVESTIGATION OF THE EFFECTS OF DUAL-ACTION SEROTONERGIC COMPOUNDS ON AFFECTIVE BIASES OF MALE RATS

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The most prevalent form of pharmacological modulation of the serotonergic system in the clinic is the inhibition of the serotonin transporter (SERT). Other approaches focus on direct manipulation of serotonin receptors, of which 5-HT6 is one of the most promising targets. Previously we showed that a 5-HT6 agonist attenuates a negative, but does not cause a positive affective bias in Wistar rats. Here, we evaluated the effects of two novel compounds caplable of simultaneous inhibition of SERT and the 5-HT6 receptor. Two groups of male Wistar rats were assessed in the Affective Bias Test in a within-subject Latin square design, where animals' affective state was manipulated with an acute administration of either MM393 (0.0; 2.5; 5.0;

7.5 mg/kg; group 1) or MM394 (0.0.; 1.25; 2.5; 5.0 mg/kg; group 2). The ability of MM393 (7.5 mg/kg) and MM394 (2.5 mg/kg) to modulate a negative affective bias (NAB) caused by 10 mg/kg of corticosterone was also tested. Both compounds slightly reduced corticosterone-induced NAB, albeit MM393 was more effective in that respect. However, 7.5 mg/kg of MM393 also caused a NAB, while MM394 was devoid of such an effect. None of the compounds showed a clearly favourable neuropsychological profile.

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TRAIT SENSITIVITY TO NEGATIVE AND POSITIVE FEEDBACK IS ASSOCIATED WITH VARIOUS ASPECTS OF ALCOHOL ADDICTION IN RATS

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Alcohol use disorder (AUD) is one of the most common psychiatric disorders. It has been demonstrated that people with AUD are abnormally sensitive to the performance feedback. However, far less is known about the role of this cognitive bias before the onset of AUD. Using a series of probabilistic reversal learning tests we classified each rat as insensitive/sensitive to negative (NF) and positive feedback (PF). Subsequently, we subjected animals to a series of intermittent-access two-bottle choice sessions. Then, using a novel instrumental second-order chained schedule of alcohol reinforcement task we examined the influence of NF/PF sensitivity on the development and maintenance of compulsive alcohol-seeking. We have also examined the interaction between feedback sensitivity and extinction/reinstatement of alcohol-seeking, and animals' motivation to drink. The behavioral studies were complemented by analyses of the levels of stress hormones and differences in the expression of potentially involved genes.

The results demonstrated that sensitivity to feedback might determine the vulnerability of rats to the development of compulsive alcohol seeking, motivation to drink, propensity to extinguish and reinstatement alcohol-seeking behaviors. They also demonstrated that trait sensitivity to feedback interacts with the levels of stress hormones and the expression of genes related to serotonergic and dopaminergic neurotransmission.

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AFFECTIVE SIGNS OF OXYCODONE WITHDRAWAL DO NOT RETAIN AFTER 14 DAYS OF ABSTINENCE IN RATS

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The study was conducted to test whether, after 14 days of abstinence from oxycodone (OXY) when the somatic withdrawal symptoms have disappeared, the increased negative affect was retained. The affect was measured as naloxone-induced place aversion and an increase in 22 kHz USV and/or a decrease in 50 kHz USV. We aimed to check whether longer abstinence from opiates is accompanied by negative affect, postulated as one of the key factors causing a relapse of opiate use. Experimental groups that received chronic oxycodone (7 days, twice daily), and two control groups – one that received chronic saline and one that received a single dose of OXY (acute withdrawal) were used. All groups underwent a conditioned place aversion (CPA) test with USV recording. All groups received naloxone (NLX) at doses that did not induce CPA in rats without opiate experience (saline group). No induction of CPA in the protracted abstinence group was found, regardless of the dose of NLX (neither 1 mg/kg nor 2 mg/kg). No expected 22 kHz USV increase and/or 50 kHz USV decrease in any of the groups was found. In OXY-dependent rats, after 14 days of abstinence, no affective signs of withdrawal were detected.

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DISULFIRAM REVERSES MORPHINE TOLERANCE BY ACTIVATING G-PROTEIN SIGNALING

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Disulfiram (DSF) is most widely known as a medication supporting abstinence in patients struggling to maintain their sobriety from alcohol. Apart from acting as a potent acetaldehyde dehydrogenase inhibitor, disulfiram was also shown to enhance opioid-induced an-

algesia as well as reverse opioid-induced tolerance and dependence. Remarkably, the molecular background of this phenomenon has not been extensively studied nor explained with only few vague hypotheses exist. Our latest work shows that disulfiram partially rescues G-protein activity in rats exposed to chronic morphine treatment, which might play a role in the suppression of analgesic tolerance to morphine. Thus, the aim of this study was to investigate the mechanism behind G-protein stimulation by disulfiram in opioid-receptor rich hypothalamus in the [35S]GTPγS assay. Our results show that disulfiram potently stimulates Gi/0 protein activity in a manner independent of μ-opioid receptor occupancy. Surprisingly, disulfiram did not significantly modulate morphine efficacy further suggesting a non-receptor site of action. We propose that disulfiram exerts this effect by covalently binding to cysteine residues to enhance GDP to GTP exchange. This notion was supported by an observation that other thiol alkylating agents – N-ethylmaleimide and SCH 202676 produced similar stimulation of G-protein activity that was reduced by dithiothreitol.

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IMPAIRMENT OF MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION IN THE BRAIN – INVOLVEMENT IN DEPRESSION?

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The brain is a structure characterized by high energy demands. Nerve cells rely mostly on the energetic support of astrocytes, which produce lactate in the process of glycolysis to be transported into neurons, where it is directly utilized in the Krebs cycle and oxidative phosphorylation. The oxidative phosphorylation system (OXPHOS), located in mitochondria, is responsible for cellular energy production *via* sequential electron transfer reactions coupled to proton translocation across the mitochondrial inner membrane. This process involves five multi-subunit complexes (Complex I-V), which in the end, produce ATP by the transfer of H+ ions across a membrane. Our aim was to investigate the levels of OXPHOS complexes and ATP in the frontal cortex and hippocampus of adult rats in an animal model of depression based on prenatal dexamethasone (DEX) treatment. In the frontal cortex, we demonstrated the diminished level of complex II, complex IV, and complex V in the DEX group which corresponds with decreased concentration of ATP in this area. Obtained results indicate that depression-like changes observed in the used animal model could be, at least in part, caused by a reduction in ATP production in the brain because it is known that depression is associated with numerous metabolic disturbances.

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POSTNATAL IMMUNE ACTIVATION WITH POLY(I:C) ALTERS ADULT MICE BEHAVIOR

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Neurodivergent people, for example people with autism spectrum disorder (ASD), ADHD or learning disabilities, often suffer from social skills deficits, cognitive impairments, and sensorimotor processing difficulties. The causes of those variations are complex, ranging from genetic predispositions to environmental circumstances, including early-life immune activation. 7-day old mice were injected with either Poly(I:C), an agent mimicking viral infection, or saline serving as control. Male mice subjected to Poly(I:C) exhibited decreased neophobia, and risk taking behavior in comparison with their saline treated counterparts. Interestingly, locomotor activity of the Poly(I:C) group was significantly higher but only in a new, potentially threating environment, contrasting with their diminished home-cage activity, as compared to the control male mice. Moreover, Poly(I:C) male mice were less likely to approach the new social stimulus, even though they tended to have more social interactions with their littermates. Our results indicate that postnatal immune activation might be involved in symptoms associated with neurodiversity.

THE INFLUENCE OF LOCOMOTOR RESPONSIVENESS TO NOVELTY ON ACTIVATION OF MICROGLIA IN THE HIPPOCAMPUS IN THE RAT MODEL OF NEUROINFLAMMATION

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Locomotor responsiveness to novelty is connected with stress susceptibility and influences peripheral immunological response. Intracerebroventricular (i.c.v.) injection of streptozotocin (STZ) induces neuroinflammation, oxidative stress and cognitive decline. The aim of the study was assessment of influence of responsiveness to novelty on number of activated microglia in hippocampal areas of rats in STZ-induced model of neuroinflammation. Rats were divided into high and low responders (HRs and LRs) in the novelty test and subsequently subjected to i.c.v. injection of STZ. Immunofluorescent assay of activated microglia (CD68+) was performed on brain slices. Significant differences between HRs and LRs were found in the CA1 area of the hippocampus in STZ-injected rats (2.5±1.22 cells/0.01 mm2 in HRs *vs.* 4.75±0.96 cells/0.01 mm2 in LRs). There were also significant differences between STZ HRs *vs.* SHAM LRs and STZ LRs *vs.* SHAM LRs animals in CA1, CA2, CA3 and DG parts of hippocampus (CA2 STZ: HR 2.25±0.96, LR 3.25±1.26; CA3 STZ: HR 4.2 ±1.64, LR 3.75 ±1.26; DG STZ: HR 3.33±1.51, LR 3.25±1.26; all SHAM groups in CA, CA2, CA3, DG 0±0 cells/0.01 mm2). Individual behavioral characteristics manifested by responsiveness to novelty influences activation of microglia evoked by i.c.v. STZ in hippocampal CA1 area involved in encoding new information.

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THE ROLE OF SHORT NEUROPEPTIDE F (SNPF) IN THE REGULATION OF THE CIRCADIAN CYCLE IN THE *TENEBRIO MOLITOR* BEETLE

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In insects, the regulation of the circadian cycle is autonomous and occurs through cooperation between a "central biological clock" in the brain and a "peripheral biological clock" in the prothoracic gland (PG). The operation of these clocks is synchronized, among other things, by external factors such as light and temperature, and is also regulated neuroendocrinally, through the cAMP–PKA–CREB signaling pathway, which is the site of action of short neuropeptide F (sNPF). sNPF is an ortholog of neuropeptide Y (NPY), which has been found in mammals as responsible among others for sleep regulation. It may be an important future research direction, as the NPY action system may be involved in the pathophysiological process of primary insomnia in humans. Insects can be models in this research. The aim of this study was to determine the role of short F neuropeptides in regulating the circadian cycle in adults of the *T. molitor* beetle, and to show that the expression level of *sNPF* gene varies when beetles were exposed to different light conditions. Furthermore, we showed that *sNPF* regulate gut physiology what again proves that it poses the same physiological properties as NPY in mammals.

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GENE EXPRESSION ANALYSIS OF SELECTED NEUROPEPTIDES OF THE BEETLE *TENEBRIO MOLITOR L.* UNDER THERMAL STRESS CONDITIONS

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Insects are the most numerous group of animals. One aspect of this wide distribution is the ability of these animals to survive in all environments and temperatures. This success is due to their high ability to tolerate a range of environmental stresses, such as low or high temperatures. Studies show that cold stress affects many physiological processes in insects. The neuroendocrine system and its associated mediators, such as neuropeptides and biogenic amines, play an important role in the regulation of physiological and behavioral processes in insects, and therefore could also potentially affect thermal tolerance. In the experiment, 30-day-old *Tenebrio molitor* beetles were used. The insects were exposed to heat stress at 40°C and cold at -5°C for one hour. The nervous system was then isolated by microsurgery. Quantification of mRNA levels for genes encoding neuropeptides such as allatostatin type C (PISCF), short neuropeptide F (sNPF) and tachykinin-related peptide (TRP) was measured by RT-qPCR. During temperature stress, both cold and heat, expression of tested genes is significantly changed in nervous tissues (brain and ventral nerve cord) of *T. molitor*.

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UNDERSTANDING THE ROLE OF CTCF IN MOUSE NEURAL PRECURSOR CELLS

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CCCTC-binding factor (CTCF) is a key regulator of chromatin organization. Recent studies indicate that Ctcf is essential for proper mouse development. CTCF depletion in mouse oocyte results in embryo death, while CTCF heterozygous mice develop tumors. CTCF expression changes during brain development. Inactivation of CTCF in mouse neural precursor (NP) cells can lead to premature neurogenesis. The mechanisms of this phenomenon are not fully defined. We found that in the mouse NP cells, acute removal of CTCF *in vitro*, upregulated expression of pro-neuronal genes including *Tubb3, Ngfr, Lrrk2, Nrp1, Insm1, Dlx1, Dlx2* while downregulating Sox9, Sox5, Hes5 which are important for astrocytic fate. To determine how CTCF may impact further development of the NP cells we grew the NP cells in conditions promoting either neuronal and astrocytic identity. Neuronal differentiation and maturation of NP cells was enhanced when CTCF was abolished. On the contrary, the CTCF – NP cells yielded two times less astrocytes as judged by the expression of Gfap+ (35% *versus* 75% of Gfap+ cells in the CTCF+ population). Our results suggest that CTCF molds the differentiation trajectory in mouse NP cells. We are currently investigating the mechanisms by which CTCF impacts proneural and astrocytic gene expression. We are particularly interested in the molecular pathways that render some loci receptive to the level of CTCF. Likewise, we would like to determine how CTCF impacts NP cell biology and how its functions may be related to the development of neurological syndromes in patients with heterozygous deletion of the *CTCF* gene.

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EVOLUTIONARY CHANGES IN THE GENETIC LANDSCAPE OF ASTROCYTES FROM PRIMATE SPECIES: A TRANSCRIPTOMIC OVERVIEW

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Astrocytes constitute the largest group of glial cells in the mammalian brain and sustain a plethora of housekeeping functions in the central nervous system (CNS). Astrocytes are crucial for synapse development, functions, and pruning. Thus astrocytes can in principle also impact high-level functions of the brain. Human and murine astrocytes differ, mouse cells feature fewer processes than their human counterparts. Despite essential function in the CNS and the possible implication the evolution of brain, the genetic bases of interspecies differences between astrocytes remain an open question. To model the evolution of astrocyte transcriptome, we profiled the transcriptomes of astrocytes derived *in vitro* from Human, Chimpanzee and Rhesus Macaque induced pluripotent stem cells. We identified 619 high confidence loci that display species specific expression level in Astrocytes; amongst them 65 are implicated in neurological disorders (NDs) including Alzheimer's disease. We are currently determining the mechanisms that might drive the differential expression of these genes. We anticipate that further investigation into the regulome of the genes displaying human specific expression pattern will help reveal key genetic changes that could account for the features of the brain specific to humans and possibly also provide new mechanistic understanding of NDs.

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TOWARDS DEFINING THE EVOLUTION OF THE REGULOME OF HUMAN ASTROCYTES

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Human astrocytes display unique features in comparison to their murine and ape counterparts. These include: increased size and complexity of the arborization pattern and enhanced calcium wave dynamics. Protein-coding genes related to human brain are largely conserved, and it has been proposed that changes in gene expression throughout primate evolution are mostly driven by changes in regulome. To model the evolution of human-specific astrocyte regulome, we took advantage of multiple computational tools and analysed Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq) data from induced plurip-

otent stem cell (iPSC)-derived astrocytes (iAstrocytes) from human, chimpanzee (Pan Troglodytes) and rhesus macaque (Maccaca mulatta). We found 11,963 regions to be more open in human than in two non-human primate species. To confim function of human enhancers, we are repurposing a lentivral Massively Parallel Reporter Assay (lentiMPRA) to allow us to interrogate function of fragments within ATAC-seq library derived from human iAstrocytes. To functionally interrogate regulatory sequences, we are employing iAstrocytes expressing dCas9-KRAB-MeCP2 introduced through lentiviral infection. Integration of this data will help us define the regulatory mechanisms that underlie the evolution of astrocyte transcriptome and thereby potentially reveal new aspects of gain of human specific brain functions.

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REGULATED EXOCYTOSIS IN ASTROCYTES CONTROLLED BY NEURONAL ACTIVITY

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Interaction between neural circuits and astrocytic processes was previously described by the concept of the tripartite synapse, which assumes that astrocytes are modulators of neurotransmission through gliotransmitters secretion. Numerous controversies arose regarding this model, therefore in our project, we want to get a better insight into the regulation of astrocytic exocytosis. We use total internal reflection fluorescence microscopy to image exocytosis events with VAMP2-pHluorin probe expressed in hippocampal cultures and in pure astrocytic ones. We show that the exocytosis frequency in astrocytes is lower in neuron/glial co-cultures than in pure astrocytic. However, electrical stimulation of mixed cultures significantly increases the rate of exocytosis. Furthermore, blocking Ca2+ release from the endoplasmic reticulum does not affect the observed effect in contrast to blocking extracellular Ca2+. In turn, blocking the neuronal activity with TTX blocks the increase in exocytosis frequency triggered by electrostimulation. To conclude, we show that the rate of exocytosis depends on the neuronal presence, and is regulated by neuronal activity probably by the influx of Ca2+ ions from the extracellular space.

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ENERGETICS AND EMERGENT CALCIUM DYNAMICS IN AN ASTROCYTE-NEURONAL NETWORK COUPLED *VIA* NITRIC OXIDE MOLECULE

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Neurons and glial cells work in conjunction during information processing in brain. Stimulation of neurons can cause calcium oscillations in astrocytes. The "glissandi" effect is associated with a decrease in infraslow fluctuations, in which synchronized calcium oscillations propagate as a wave in hundreds of astrocytes. In this work, defining an astrocyte-neuronal (A-N) unit as an integrated circuit of one neuron and one astrocyte, we developed a minimal model of neuronal stimulus dependent calcium oscillations in astrocytes. Incorporating inter-unit communication *via* nitric oxide molecules, a coupled network of 1,000 such A-N units is developed in which multiple stable regimes were found to emerge in astrocytes. Present study is intended to explore the emergence of calcium waves in astrocytes by nitric oxide molecule in a couple ensemble of A-N network. Herein, we observe synchronization between astrocyte's calcium oscillations which are dependent upon neuronal stimulus and coupling strength. We examined the ranges of neuronal stimulus and coupling strength between A-N units that give rise to such dynamical behaviors. We also report that there exists a range of coupling strength, wherein units not receiving stimulus also start showing oscillations and become synchronized. Our results support the hypothesis that "glissandi" like phenomena exhibiting synchronized calcium oscillations in astrocytes help in efficient synaptic transmission by reducing the energy demand.

MUTATIONS OF BETA2 H267 RESIDUE OF GABAA RECEPTOR TRANSMEMBRANE DOMAIN AFFECT GATING TRANSITIONS DURING RECEPTOR ACTIVATION

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In the adult mammalian brain GABA is the major inhibitory neurotransmitter. GABAA receptor (GABAAR) most typically consists of 2α, 2β and γ2 subunit with two orthosteric binding sites at the α/β interface. Recent structural studies largely determined the static structure of GABAARs, however precise molecular scenarios underlying conformational transitions remain unclear. To address this issue our group studied the impact of specific mutations on GABAAR functioning. One of these residues is histidine (H) in position 267 of β2 subunit, located at the second segment (M2) of transmembrane domain (TMD) of GABAAR. This residue is close to the channel gate and forms a part of an anesthetic binding site being also important for αβ receptor modulation by H^+ and Zn^{2+}. In the present study we used macroscopic (with ultra-fast perfusion) and single-channel patch-clamp recordings together with model simulations to investigate the impact of the α1β2H267K/A/C/Eγ2L substitutions (compared to WT). Analysis of responses evoked by rapid GABA applications showed that this mutation strongly enhanced macroscopic desensitization for β2H267K mutant. However, single-channel recordings revealed that mutation of H267 affected not only desensitization but also openings/closings and preactivation. Hence, the H267 residue of M2 segment is involved in all conformational transitions underlying GABAAR gating.

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MOLECULAR PATH OF THE GABA TYPE A RECEPTOR ACTIVATION

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GABA type A receptor, a pentameric ligand gated ion channel, plays a crucial role in inhibition in the brain and its dysfunction may cause various diseases. Upon the agonist binding at the extracellular site, the receptor undergoes a series of transitions leading to the opening of the transmembrane channel gate allowing the ions to flow into the neuron. The molecular mechanism of the receptor activation is not known. We used molecular modeling, mutagenesis, electrophysiology and kinetic modeling to elucidate it. Our results indicated that mutations of the residues at the binding site are influencing the binding related transitions to a higher extent than those located in other regions. On the contrary, the rates of the transitions in the bound states tend to be affected by nearly all mutations, in a manner not clearly dependent on structural localization. Also, the timeline of those transitions was estimated – two synchronized components were revealed: the first one composed of movement of the residues located at N-terminal, agonist binding site and domain interface and the second one made of remaining areas. Thus our data indicated the allosteric character of the receptor activation, characterized by significant cooperation and synchronization of the respective protein regions.

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DISTINCT REGULATION OF GABAERGIC TRANSMISSION AND PLASTICITY ONTO INTERNEURONS IN THE CA1 REGION OF HIPPOCAMPUS – ROLE OF INTEGRINS

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Integrins are a family of heterodimeric cell adhesion receptors playing a role in the regulation of excitatory synaptic plasticity and glycinergic synapses efficacy. We have recently shown that inhibitory GABAergic transmission and plasticity onto pyramidal cells strongly depends on integrins in hippocampal CA1 network. However, their role in the plasticity of inhibitory transmission onto interneurons still await elucidation. We therefore investigated the impact of integrins on GABAergic transmission measured from two distinct classes of hippocampal interneurons: parvalbumin (PV) and somatostatin (SST). We recorded miniature inhibitory postsynaptic currents (mIPSCs) using patch-clamp recordings in acute slices from PV-tdTomato and SST-tdTomato mice. We observed that, in the presence of GRGDSP peptide, mIPSCs amplitude measured from PV fast spike (FS) cells, PV non-fast (nFS) spike interneurons located in St. pyramidale and SST interneurons was significantly potentiated (108 ± 1 %, n=5; 113 ± 7 %, n=5; 121 ± 5 %, n=10). On the contrary, GRGDSP application onto nFS interneurons in St. radiatum led to significant decrease of GABA-ergic transmission (91 ± 3%, n=7). We provide the first evidence that integrins are involved in plastic changes of GABAergic synaptic transmission depends on cell type.

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INTERPEDUNCULAR NUCLEUS NEURONS INNERVATED BY NUCLEUS INCERTUS ARE SENSITIVE TO NICOTINE – A NEW NEURONAL SUBSTRATE FOR THE INFLUENCE OF STRESS ON NOVELTY PREFERENCE

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The correct response to novel stimuli has a significant influence on our proper functioning. A crucial role in familiarity/novelty signaling plays the interpeduncular nucleus (IPN) along with the medial habenula and dopaminergic neurons of the ventral tegmental area. The main factor leading to the development of disorders resulting from inadequate response to novelty is stress. One of the highly stress-sensitive brain structure is the nucleus incertus (NI) which is the main source of neuropeptide relaxin-3 (RLN3) in the brain. Therefore, it is believed that the NI – IPN connection is a part of a neuronal mechanism involved in stress related novelty preference disturbances. Therefore, we aimed to verify the impact of familiarity signaling nicotine, on the activity of IPN neurons that are directly innervated by NI neurons in rats. With the use of optogenetics and electrophysiological whole-cell-patch-clamp recordings of IPN neurons activity we showed that IPN neurons innervated by NI are sensitive to nicotine, which implies a role of NI – IPN axis in the familiarity signaling. Moreover, using viral based fluorescent staining we showed that NI-originating fibers in the IPN contain RLN3, what indicate the NI as the main source of this neuropeptide in the IPN.

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AVERSIVE STIMULUS CODING REVISITED – BRAIN STATE-DEPENDENT RESPONSES OF REWARD AND ANTI-REWARD SYSTEMS TO ELECTRICAL FOOT SHOCK

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Dopaminergic (DA) neurons of ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) code information about aversive stimuli (AS). One of VTA/SNc inputs involved in AS-coding comes from lateral habenula (LHb). In both VTA/SNc and LHb two neuronal populations have been distinguished based on the type of responses (excitatory or inhibitory) to AS. Given that basal activity of VTA/SNc DA neurons depends on alternating brain states under urethane anaesthesia, we checked whether VTA/SNc DA neurons responses to AS are also brain state-dependent. Additionally, we wanted to examine if basal activity of LHb neurons and their responses to AS differ between brain states. Firstly, we performed *in vivo* extracellular recordings of midbrain DA neurons combined with optotagging and recorded their responses to electrical foot shocks from urethane anaesthetized rats. Secondly, we recorded activity and responses to AS of LHb neurons using Multi-Electrode Arrays. We observed two neuronal subpopulations of both VTA/SNc and LHb – excited and inhibited by AS. However, we also recorded previously undescribed populations of VTA/SNc and LHb neurons which responses to AS differ between brain states. This study sheds new light on interplay of LHb/VTA/SNc in AS-coding and influence that brain state may exert on processing of aversion.

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PENTYLENETETRAZOLE–INDUCED KINDLING AS A MODEL OF METABOLIC SYNDROME

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Data on the relationship between epilepsy and metabolic syndrome justified the evaluation of MS markers expression in PTZ-kindled rats. PTZ kindling was induced in four months aged male Wistar rats with three weeks epileptogen (35.0 mg/kg, i.p.) administration. Those animals with fully developed generalized seizures were used for investigations. The glucose tolerance test (GTT) was followed by a significant rising in blood glucose level 30 min after glucose i.p. administration (2.0 g/kg) up to 395.7+47.2 mg/dl), which exceeded the control data by 1.74 times ($P<0.001$). Insulin tolerance test (0.75 U of insulin/kg) revealed in 15 min after glucose i.p. administration (2.0 g/kg) up to 114.3+15.7 mg/dl), which exceed the control data by 31.3% ($P<0.001$). Significant differenc-

es were maintained for 2 h. Avidin-biotin peroxidase complex method was used to determine differences in the immunohistochemical determination of TNF-α and p-NF-kB in dorsal hippocampal structures. It was established that in kindled rats, the level of TNF-α and p-NF-kB determined with the intensity of color raised in PTZ-kindled rats by 3.73 and by 3.0 times correspondently (P<0.001). Circulating fasting blood triglycerides was 142.2+22,6 mg/dl and exceeded the control value by 18.8% (P<0.01). Gained data favored similar mechanisms of chronic brain epileptic activity and metabolic syndrome.

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ABNORMAL METABOLISM AND AUTOPHAGY IN THE SPINAL CORD OF SOD1-G93A MICE ARE MODIFIED BY SWIM TRAINING

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Amyotrophic lateral sclerosis (ALS) is an incurable, neurodegenerative disease. ALS might cause behavioral disturbances and cognitive dysfunction. Exercise has revealed a neuroprotective influence on the motor neurons in ALS. Swim training was applied five times per week for 30 min to the SOD1-G93A mice model of ALS and B6SJL mice as controls. ALS mice were tested before ALS onset, at the first symptoms of the disease, and at the terminal stage. All mice underwent behavioral tests. The spinal cord was tested for enzymatic activities and signaling protein content. The study revealed increased locomotor activity in pre-symptomatic ALS mice; the swim training reduced these symptoms. Decreased PGC-1α, IGF-1, and TBK1 signaling molecule content, among with increases in AMPK, metabolic sensor, abnormally regulated metabolism, and autophagy in the spinal cord of SOD1-G3A mice, causing accumulation of p62 and mitochondrial OGDH. The metabolic changes present already at the pre-symptomatic stage of the disease shift towards glycolytic processes at the terminal phase of ALS. On the other side, we suggest that swim training causes the adaptation resulting in higher NFL content and increased IGF-1, protecting spinal's cord mitochondria against disruption. The therapeutic aquatic activity might slow down the progression of ALS.

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ACTIVATION OF NON-NUCLEAR ESTROGEN RECEPTORS PROTECTS MOUSE NEURONS AGAINST B-AMYLOID-INDUCED CASPASE-DEPENDENT APOPTOSIS

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Alzheimer's disease (AD), is an age-related neurodegenerative disorder described by the progressive deterioration of memory and cognitive functions. It is characterized by extracellular β-amyloid plaques and intracellular neurofibrillary tangles along with accompanying synaptic and neural loss. Since currently available therapies provide only moderate symptomatic relief without affecting AD progression, novel treatments are needed. Estrogen receptors (ERs) are widely known for their neuroprotective potential. In recent years, it has been noticed that the differences in nuclear and non-nuclear ERs activation mechanisms position non-nuclear ERs as a safer alternative that, so far, seem devoided of nuclear ER activation ramifications such as the increased risk of cardiovascular diseases and accelerated progression of hormone-dependent cancers. In this study, we demonstrated that PaPE-1, a compound that has been synthesized to selectively target non-nuclear ERs, is an effective neuroprotectant in the cellular AD model. Neuroprotective effects of PaPE-1 on primary neocortical neurons treated with β-amyloid have been verified in the context of apoptosis, by mitochondrial membrane potential measurement, caspase-3, -8 and -9 activities assessments, and the measurements of apoptosis-related mRNAs and proteins such as Fas/FAS, FasL/FASL, Bax/BAX, Bcl2/BCL2 and Gsk3b/GSK3β. Obtained results provide evidence that preferential activation of non-nuclear ERs with PaPE-1 protects brain neurons against β-amyloid-induced toxicity.

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ALTERED SYNAPTIC PHYSIOLOGY AND IMPAIRED COGNITION, RESPONSE TO NOVELTY AND MOTOR BEHAVIOR IN A RODENT MODEL OF ACCELERATED AGING

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Aging causes changes in synaptic physiology as well as cognitive decline and impaired motor function. We evaluated the relation between motor function, cognitive performance and selective synaptic markers in natural aging and a rat model of accelerated aging (AA). AA was induced by D-galactose (250 mg/kg) administration to 12-week-old rats for 40 days and matched to Sham (saline injections) and 4 – 21-month old (natural aging) rats. Behavioral evaluation was performed with the open-field test; rotarod, and water maze. Novelty responses were evaluated by the novel object recognition test1 and the mismatch novelty test2. Hippocampal expression of synaptic markers and markers of aging-associated altered synaptic plasticity was evaluated in hippocampal membranes by western blot. AA rats showed impaired exploration, motor performance, mild cognitive impairment and mismatch novelty responses compared to sham controls but less pronounced that naturally aged rats. AMPA GluA1/GluA2 ratio, PSD-95 and gephyrin were mildly decreased in D-Gal and naturally aging rats while monoaminergic markers were differently altered in D-Gal *vs.* natural aging. Altogether this suggests that aging-like pathology observed in this model does not fully reproduce the physiological responses to aging.

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STIM2 REGULATES NMDAR ENDOCYTOSIS AFTER ITS OVERACTIVATION

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STIMs are calcium (Ca2+) sensors localized in the endoplasmic reticulum (ER). They play a role in store-operated Ca2+ Entry (SOCE), which is described as Ca2+ influx in response to the ER Ca2+ store depletion. While the main function of STIM1 is to contribute to SOCE, STIM2 is considered to be the basal Ca2+ level regulator. Apart from the participation in SOCE, STIMs also perform non-canonical functions, for instance, regulation of Ca2+ influx *via* NMDARs. Since Ca2+ overload and NMDAR over-activation are hallmarks of many neurodegenerative diseases, we aimed to investigate whether STIMs may also regulate NMDAR endocytosis and thus protect neurons from Ca2+ overload. Co-immunoprecipitation and immunofluorescence experiments showed that the formation of STIM-NMDAR complexes increased after NMDAR endocytosis. Although STIM silencing with lentiviruses did not affect total NMDAR counts, by examining surface proteins and synaptosomes we observed that STIM2 knockdown reduced NMDAR endocytosis. Our results may suggest that STIM2 (but not STIM1) may take part in the regulation of NMDAR endocytosis. Further studies are needed to understand the mechanism underlying this regulation, which could contribute to a better understanding of neurodegenerative diseases in the future.

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EXTRACELLULAR SIGNAL-REGULATED KINASE 1 (ERK1)-MEDIATED PHOSPHORYLATION OF VOLTAGE-DEPENDENT ANION CHANNEL (VDAC) SUPPRESSES ITS CONDUCTANCE

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ERK1 is one of the members of the mitogen-activated protein kinases that regulate important cellular functions. VDAC is located at the outer membrane of mitochondria. Here, an interaction between VDAC and ERK1 has been studied on an artificial planar lipid bilayer using *in vitro* electrophysiology experiments. We report that VDAC is phosphorylated by ERK1 in the presence of Mg2+-ATP and its single-channel currents are inhibited on the artificial bilayer membrane. Treatment of Alkaline phosphatase on ERK1 phosphorylated VDAC leads to partial recovery of the single-channel VDAC currents. Later, phosphorylation of VDAC was demonstrated by Pro-Q diamond dye. Mass Spectrometric studies indicate phosphorylation of VDAC at Threonine 33, Threonine 55, and Serine 35. In a nutshell, phosphorylation of VDAC leads to the closure of the channel.

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POLYMERS IN THE SERVICE OF NEUROSCIENCE

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Nowadays among many available methods, nerve tissue engineering (NTE) is one of the applicable methods to reconstruct damaged nerve tissues. The crucial element of the effective medical system is apllied material. Conducting polymers are promising materials for tissue engineering applications, which results from their inherent ability to enable charge carriers movements. Owing to their electrical activity and reversible doping process they can transmit electrical and mechanical stimuli. Moreover they provide a biocompatible scaffold that can serve as physical support for living cells. The aim of the study was to determine the possibility of polymerization of pyrrole to deposit layers that could be utilized as functional wires to replace damaged nerves. In the work, several aspects of materials for bioelectronics applications are considered and discussed. These are synthesis protocols, oxidation state, chemical and mechanical stability to mention only a few. Moreover, insight into mechanical properties like scratch resistivity or adhesion ability are discussed, which are crucial for perspective coating application.

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METACOGNITION AND COGNITIVE CONTROL: CONSCIOUS ERROR DETECTION IN CONFLICT CONDITIONS

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Cognitive control consists of many processes that collectively lead to the planning and coordinating of human behavior to achieve the goal. Similarly, metacognitive processes include knowledge and cognitive processes that monitor or control human cognition. Previous studies have shown the importance of metacognitive processes in mental adaptation. However, the impact of congruence on the ability to consciously detect errors remains poorly understood. In the current study (n=34), we used the modified Stroop task with a confidence scale to investigate the relationship between cognitive adaptation and the ability to detect errors consciously. We distinguish between inducer items that trigger adaptive control and diagnostic items that measure the effects of adaptive control on performance to minimize confounds related to low-level learning. We performed a two-way repeated measure ANOVA testing the impact of congruence and congruence in the preceding trial on the accuracy for trials where subjects were confident they had responded correctly. The results show a significant and robust interaction effect. These results indicate that metacognitive processes (error detection) adapt to current circumstances, such as the presence of a conflict. We conclude that the ability to detect errors in conflict conditions consciously depends on earlier detection of the conflict.

GETTING READY FOR ACTION! RESPONSE REQUIREMENTS MODULATE OSCILLATORY DYNAMICS UNDERLYING ANTICIPATORY ATTENTION

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It has been argued that specific response requirements concerning a to-be-selected object may influence attentional processes. Brain oscillations reflected in the electroencephalogram (EEG) may provide important insight into processes underlying such action-attention functional relations. In this study, we employed two versions of an endogenous orienting task with symbolic spatial cues: a stimulus detection task with no-choice responses, and a stimulus discrimination task with two-choice responses. The analysis was focused on EEG activity during an anticipatory stage of spatial orienting. Dominant sources of oscillatory activity in frontal, motor, and visual areas were assessed with the generalized eigendecomposition (GED). Phase coherence between these sources was computed as a measure of functional connectivity. The EEG power results showed: stronger desynchronization of alpha power over visual areas contralateral-to-attended space in the discrimination task; earlier response selection in the detection task reflected in beta desynchronization over motor regions. The connectivity results showed task differences in terms of the strength of phase coherence across parietal-visual connections in alfa-band ipsilaterally-to-attended space, and the number of significant connections in alpha band over frontal-parietal network The obtained results suggest that action demands shape attentional processes in terms of both local oscillatory activity and inter-regional connectivity.

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ELECTROPHYSIOLOGICAL CORRELATES OF AUDITORY AND VISUAL AWARENESS: IN SEARCH FOR DOMAIN-SPECIFIC AND DOMAIN-GENERAL MECHANISMS OF CONSCIOUS PERCEPTION

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The ongoing debate as to whether neural correlates of consciousness (NCCs) are related to early activity in sensory-specific cortical regions or to late activity in higher-order brain regions remains unresolved. We propose a more general approach investigating domain-specific and domain-general mechanisms involved in conscious perception, that may confound NCCs research. We investigated the relationship between electrophysiological correlates of visual and auditory awareness by conducting two experiments. Visual (Gabor patch presented in the centre of the visual field) and auditory (simple tone presented binaurally) stimuli were presented at individual thresholds (staircased – critical trials). Additionally, control trials (containing a stimulus presented above the calibrated threshold level) and catch trials (no tone or Gabor patch) were presented. In every trial, participants performed an objective detection task and rated their subjective perception using the PAS. Behavioral results suggest that subjective judgments are more multimodal – a similar PAS ratings distribution was observed in both modalities. The objective task performance depends more on the modality – despite the staircase, we observed higher accuracy for the auditory than for the visual task. ERPs results are under analyses and will be presented at the conference. We will focus on the differences in VAN/AAN and P300 components between modalities.

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FOREST BEFORE TREES, OR TREES BEFORE FOREST? TEMPORAL HIERARCHY OF GIST AND OBJECT RECOGNITION IN SCENES

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How does the representation of a scene develop over time? It is well established that gist and general meaning of a scene can be recognized rapidly, but recognition of objects can also be extremely fast. Importantly, because previous studies focused on recognition of one aspect only – either gists or objects – direct comparisons between them, crucial to elucidate the temporal hierarchy of scene perception, are missing. To fill this gap we investigated and directly compared recognition speed of backgrounds and objects in scenes. We used images depicting either a natural or a man-made background and a single natural (animal) or man-made (furniture) foreground object, combined in congruent or incongruent ways. Scene images were displayed briefly (67 ms) and participants (n=31) performed four blocks of a speeded Go/no-Go task. In two blocks they classified backgrounds (in one natural was a target and man-made a distractor, in the other vice versa), while in the other two they classified objects. We found that both reaction-times and event-related potential latencies were shorter for objects as relative to backgrounds. Therefore, our study indicates that the visual system can classify local objects before global gist, providing further evidence in favor of the local-to-global theories.

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MOTOR ACTION INFLUENCE ON VISUAL AWARENESS

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The relation between motor actions and visual awareness has recently gained a significant interest. The study investigated how unrelated to presented stimuli motor action influenced perception of that stimuli. The experiment used a backward masking paradigm in which a visual cue prompting motor action execution or inhibition was presented immediately after the stimulus displayed for perceptual discrimination task. After the motor response participants rated their visual awareness of the stimulus using the Perceptual Awareness Scale and performed a discrimination task. The results showed that motor action inhibition increased both the stimulus awareness ratings and the accuracy performance in the discrimination task as compared to the condition of motor action execution. Obtained results suggest that the inhibition of motor action influences the visual awareness in a greater extent than motor action execution, although this effect requires additional verification.

SENSORY MODALITY DEFINES THE RELATION BETWEEN EEG LEMPEL-ZIV DIVERSITY AND MEANINGFULNESS OF A STIMULUS

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Diversity of brain activity is a robust neural correlate of the global states of consciousness. It has been recently proposed that diversity measures specifically reflect richness and differentiation of conscious experience. In line, previous studies found that perception of meaningful visual stimuli, causing richer and more differentiated experiences, caused greater brain signal diversity than perception of meaningless stimuli. To investigate whether this relation is consistent across sensory modalities we used naturalistic visual and auditory stimuli (movies and audiobooks) and presented them to participants in three versions varying in the amount of meaning (original, scrambled, and noise) while recording EEG signals. We report three main findings. First, greater meaningfulness of the visual stimulus was related with higher Lempel-Ziv diversity of EEG signals, but a reverse effect was found in the auditory modality. Second, visual perception was related with generally higher EEG diversity than auditory perception. Third and relatedly, perception of meaningful visual stimuli resulted in higher, while perception of auditory stimuli in lower EEG diversity in comparison to the resting-state. In conclusion, brain signal diversity depends on the stimulated sensory modality, and thus is not a generic index of the richness and differentiation of conscious experience.

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DISENTANGLING EEG CORRELATES OF CONSCIOUSNESS AND ATTENTION. THE EFFECTS OF CUEING ON DETECTION, IDENTIFICATION AND ERPS

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It is relatively uncommon to employ precise attentional manipulations into consciousness research to investigate whether those manipulations change conscious experience. Therefore, the present work is to examine whether the activation of orienting and alerting attentional networks might influence its level. To achieve this goal, an experiment utilizing the threshold presentation of Gabor patches combined with the Posner cueing paradigm was conducted (N=100). The attentional cue was a black star. The experiment consisted of four cue conditions: location cue (always predictive to the target), central cue (presented at the fixation cross location), multiple cue (stars appeared simultaneously in four possible target locations) and no-cue. After the cue presentation, the Gabor patch target was presented in one out of four possible locations and in one of four possible orientations (of the stripes' tilt). Subsequently, participants were asked what was the target location (detection task) and orientation (identification task). Finally, participants were asked to give a PAS rating a subjective awareness measure. The results show that the most pronounced attentional effects occur with the lowest visibility judgments (when participants claim they do not see any stimuli). Both attentional networks exert influence on objective and subjective performance. The orienting network, however, influences PAS ratings more in the detection task, rather than the identification task. Further analyses will be performed on EEG data to investigate how these effects are reflected on the neural level. We plan to focus on changes in VAN and P300 components between attentional networks.

SILENT MOVIES SYNCHRONIZE SECONDARY AUDITORY CORTICES MORE IN EARLY DEAF THAN HEARING INDIVIDUALS

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The auditory cortex of deaf individuals responds to a range of visual tasks. Still, the nature and extent of this repurposing is not well understood. Here naturalistic stimuli were used to elicit neural synchrony in early deaf (n=21) and hearing individuals (n=22). Participants passively watched an animated movie (The Triplets of Belleville) without sound and three distorted versions of the same film that disrupted its meaning: two temporal piecewise-scrambled versions lacking a coherent plot (12 s and 2 s scrambled) and one visually distorted (diffeomorphic) lacking any meaning. In both groups, early visual cortices were synchronized to a similar degree across stimulus types, while high-

er-cognitive areas (e.g., precuneus, superior parietal lobule and prefrontal cortex) were more synchronized by the intact, meaningful version of the movie. Secondary auditory cortices, along the extent of the superior temporal sulcus (STS), exhibited higher synchrony in deaf than in hearing participants across all stimulus types, with larger effects in the right hemisphere and little synchrony in A1. Meaningful stimulus elicited a significantly higher STS synchronization across deaf individuals than all three scrambled conditions. In the absence of early auditory experience, the STS is engaged by meaningful visual narratives.

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THE IMPACT OF SENSORY SUBSTITUTION DEVICES ON BRAIN PLASTICITY OF THE BLIND INDIVIDUALS: A CASE STUDY

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Sensory substitution devices (SSDs) can translate information from one kind of sensory input to another, e.g., present visual information through sound or touch. Recent studies show the superior ability of the congenitally blind to use such devices to navigate new environments and detect the size and shape of objects. Here, we investigated how prolongated training with SSDs can influence the brain of a blind individual. Four blind adults participated in four-week training with two SSDs: BrainPort (transforming visual information into tactile), and Colorophone (transforming visual information about colours into auditory). Additionally, they participated in two MRI scans, pre- and post-training, where we acquired resting-state and task-based fMRI data. During task-fMRI participants listened to sounds representing colour information in the Colorophone, i.e., sounds that they have become familiar with during training-phase. After training with SSDs, fMRI results showed increased activation in the motor cortex (precentral gyrus and postcentral gyrus) and the right superior temporal gyrus. Moreover, the resting state fMRI analyses suggest increased functional connectivity between the temporal lobe and motor cortex. These results, although shown in an explanatory manner, are consistent with the nature of training and suggest development of sensorimotor contingencies as a result of the training.

TUBEROUS SCLEROSIS COMPLEX IS ASSOCIATED WITH DIMINISHED NEURAL RESPONSE TO AFFECTIVE TOUCH

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Tuberous sclerosis complex (TSC) is a rare genetic disease with a high risk for developing autism spectrum disorder (ASD). Deviations in several brain functions are implicated in both TSC and ASD. For the first time, we explored whether altered processing of affective touch, related to ASD, can also be observed in TSC patients without ASD symptoms. Three groups of children, patients with TSC and ASD (n=10), patients with TSC without ASD (n=10) and typically developing children (TD, n=20), participated in the fMRI study. The participants were gently struck with a soft brush on the arm and palm, which are associated with affective and non-affective touch, respectively. Contrasting the BOLD response to affective *versus* non-affective touch revealed activation within the orbitofrontal cortex (OFC) in the TD group, while no suprathreshold activation was observed in TSC groups. As the OFC is involved in affective touch processing, the results showed that TSC is related to diminished neural response to affective touch, regardless of ASD diagnosis. This further suggests that TSC can be an attractive model to study autistic traits.

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THE NEURAL CORRELATES OF SPATIAL SOUND LOCALIZATION BASED ON THE PRESTIMULUS OSCILLATORY BRAIN ACTIVITY IN COCHLEAR IMPLANT USERS

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The ability to locate the source of a sound is critical for survival. Thanks to spatial hearing it is possible to distinguish among different sound sources in complex acoustic environments. Consequently, impairments and loss of hearing affect orientation in space, and communication. This study aimed to investigate the role of prestimulus oscillatory activity in spatial sound localization. The oscillatory brain activity in cochlear implant users had been recorded during the performance of a specially designed sound localization task. The prestimulus power spectrum had been computed between trials, where spatial sound localization task was performed correctly and those in which subjects failed to indicate the correct sound's source. To provide anatomical specificity, the source analysis was conducted, employing the beamforming method. Sensor level statistics showed no significant differences in power spectra. However, source analysis revealed several significant unilateral brain areas correlating with the ability to localise sound in space, i.e., the precuneus, postcentral gyrus, cingulate cortex, posterior parietal cortex, at 4 Hz. It can be reasonably assumed that these cortical regions are crucial for spatial sound localization performance. Moreover, found unilaterality stresses out the importance of the right hemisphere in spatial sound localization.

40 HZ AUDITORY STEADY-STATE RESPONSES AS POTENTIAL BIOMARKER OF AWARENESS IN THE PROLONGED DISORDERS OF CONSCIOUSNESS

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We used the auditory steady-state responses (ASSR) method with 40 Hz frequency modulation to verify whether it can be used as a diagnostic indicator in determining the level of consciousness in patients with prolonged disorders of consciousness (pDoC) after severe brain injury. The clinical group included 44 pDoC patients whose diagnosis was based on repeated administration of Coma Recovery Scale-Revised (CRS-R), and was split based on the symptoms of awareness. The control group included 20 healthy volunteers. To induce ASSRs, 40 Hz stimulation was used with multiple presentations of short 500 ms long series of a white-noise bursts ('clicks') with frequency modulation of 40 Hz. The ITPC (inter-trial phase clustering) indicator was used as a measure of ASSR response. We found significant differences in the mean ASSR 40 Hz response between the groups of aware pDoC patients, unaware patients, and the control group. Positive correlations between ASSR 40 Hz and the patient's best total CRS-R score as well auditory, visual, motor, oromotor-verbal functions, and communication subscale best scores were also observed. Research indicates a potential role of the auditory 40 Hz steady-state responses as a biomarker of consciousness in the process of diagnosing the level of consciousness of pDoC patients.

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THE SELF AND A CLOSE-OTHER: HOW DO PROCESSING OF FACES AND NEWLY ACQUIRED INFORMATION DIFFER?

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Self-related information (e.g., self-face) are preferentially processed and this phenomenon may be driven by its extreme familiarity. However, the findings of numerous behavioral studies reported a self-preference for initially unfamiliar information, arbitrarily associated with the self. In this study, the neural underpinnings of extremely familiar stimuli (self-face, close-other's face) and stimuli newly assigned to one's own person and to a close-other (abstract shapes) were investigated. Control conditions consisted of unknown faces and unknown abstract shapes. P3 amplitude to the self- face was larger than to close-other's and unknown faces. Nonparametric cluster-based permutation tests showed significant clusters for the self-face *vs.* close-other's face and self- face *vs.* unknown faces comparisons. Nevertheless, in the case of shapes P3 amplitude to the self-assigned shape and P3 amplitude to the shape assigned to the close-other were similar, and both were larger than P3 to unknown shapes. No cluster was detected for the self- assigned shape when compared with the shape assigned to the close-other. We suggest this lack of differences may be mainly driven by similar attentional biases to self-assigned shapes and shapes assigned to the close-other.

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PRE-STIMULUS A POWER PREDICTS BOTH OBJECTIVE TASK ACCURACY AND SUBJECTIVE PERCEPTUAL AWARENESS

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Previous research has consistently shown that the power of spontaneous alpha-band oscillations (7-14 Hz) directly preceding a visual stimulus predicts whether it will be perceived or not. However, given that objective task performance and subjective conscious experience may be dissociated, it is not clear how alpha oscillations affect these two aspects of perception. To address this question we conducted three experiments (total n=320) in which stimuli were presented at individual thresholds with different complexity of stimulus. In every trial, participants performed an objective identification task and rated their subjective perception using the Perceptual Awareness Scale (PAS). Impact of the pre-stimulus alpha power on tasks performance and subjective experience was modeled on a single-trial level. Analysis of data from the two Gabor patch experiments indicate that high pre-stimulus alpha-power was related to worse accuracy in the identification task, and to lower PAS ratings (i.e., weaker subjective awareness). Importantly, we found the effects of accuracy and alpha-power on the PAS to be independent. In conclusion, by testing a big sample of participants, employing stimuli of varying complexity, and different methods of controlling awareness we revealed that pre-stimulus alpha-band power is robustly related to both objective task performance and subjective awareness.

STRIATAL ACTIVITY FLUCTUATIONS AFFECT SUBSEQUENT SELF-CONTROL DECISION MAKING

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The brain activity directly related to the decision making process has been studied extensively. Only a few studies showed that the reward system activity preceding choice affects decision making. However, no similar studies on such activity fluctuations (endogenous or driven by external stimuli) in the context of self-control decision making have been conducted. To fill the gap, we studied how the fluctuations in striatal activity (essential to the reward system) influence subsequent dietary self-control. We checked whether striatum activity prior to food choice (≤ 3000 ms) affects the probability of successful self-control and the self-control decision strength (assumed to be greater for faster successful and for slower failed self-control decisions). Thirty-six participants rated the healthiness and tastiness of foods. In the fMRI scanner, they made 120 choices with self-control challenges (healthier *versus* tastier foods). Our analysis revealed higher putamen activity prior to the choices with successful self-control as compared to the activity prior to failed self-control. Moreover, we showed correlation of the pre-choice putamen activity with the self-control decision strength. Our findings suggest that self-control performance is influenced by the preceding striatum activity. Spontaneous fluctuations in striatal activity may be one of the mechanisms underlying inconsistencies in human decisions.

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THE RELATIONSHIP BETWEEN TEMPORAL INFORMATION PROCESSING IN MILLISECOND RANGE AND EXECUTIVE FUNCTION IN YOUNG NORMAL ADULTS

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A number of data has indicated that temporal information processing (TIP) constitutes an underpinning for many mental functions, like language, attention, memory, and planning which may be studied as an example of executive function. Efficient planning ability involves initial thinking time (ITT) to plan a sequence of sub-goals. As this preplanning strategy is cognitively demanding, it may be expected that subjects characterized by more skilled TIP indicate longer ITT and, in a consequence, the higher accuracy of planning ability. The aim of this study was to verify whether the relation between TIP in some tense of milliseconds and planning is mediated by such ITT. 110 young, healthy adults (Mage=23 years) participated in this study. To assess the efficiency of TIP and

planning ability, the auditory temporal-order judgment task and the Tower of London – Freiburg version were applied, respectively. The relations between TIP and ITT were tested using mediation analysis. The results indicated a significant direct effect of TIP on planning ability, as well as a significant indirect effect of such TIP on planning *via* ITT. These results indicated that high resolution in millisecond time domain may provide a neural base for the efficient executive functioning.

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THEORY OF MIND IN TEACHERS – PRELIMINARY RESULT FROM A NEUROIMAGING STUDY

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In all social interactions, we rely on our exceptional ability to understand the minds of others. This ability is the theory of mind (TOM), which allows understanding emotions, beliefs, desires, goals, and intentions of others. Most studies concerning TOM focus on children or clinical populations. The teacher-child relationship is thought to be crucial in education and it is related to students' academic achievements and classroom behavior. Thus, here we focused on TOM abilities in a group of primary school teachers. We tested differences between teachers (TC) and a control group (C) in TOM abilities in relation to children and adults. We designed a false-belief task with stories regarding adults and children respectively. At the behavioral level there were no between-group differences in accuracy. At the neuronal level, we observed a decreased activation in the left inferior frontal gyrus and superior temporal sulcus in the TC group, in children stories compared to adult stories. The opposite was observed in the C group. Lower activity in TOM network in teachers, during child story condition may correspond to work-related specialization. The results are still preliminary and should be treated with caution.

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AMBIGUITY OF THE TOWER TASKS

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Tower tasks (TT) are often used as tests for planning and recursive problem solving. They are also used as examples of so-called cognitive skills. However, plurality of versions of TT and difficulties in operationalisation of planning and counterfactual thinking makes using TT difficult. The aim of this presentation is to show the results of meta-analysis performed on research papers reporting the results of studies conducted on neurodegenerative patients with usage of TT. The articles were analysed with regards to characteristics of dysfunctions of the patients and version of the TT. Based on this analysis, two crucial observations have been made. Firstly, plurality of solving strategies implies that TT does not always test recursive problem solving and planning. Secondly, differences in the structure of the problem imply that puzzles which require an equal number of movements to solve vary in difficulty. Concluding, these nuances indicate heterogeneity of cognitive functions which are tested with TT. The version of the task and arrangement of the initial and goal states in a given trial has to be taken into account when assessing abilities of planning and recursive problem solving.

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