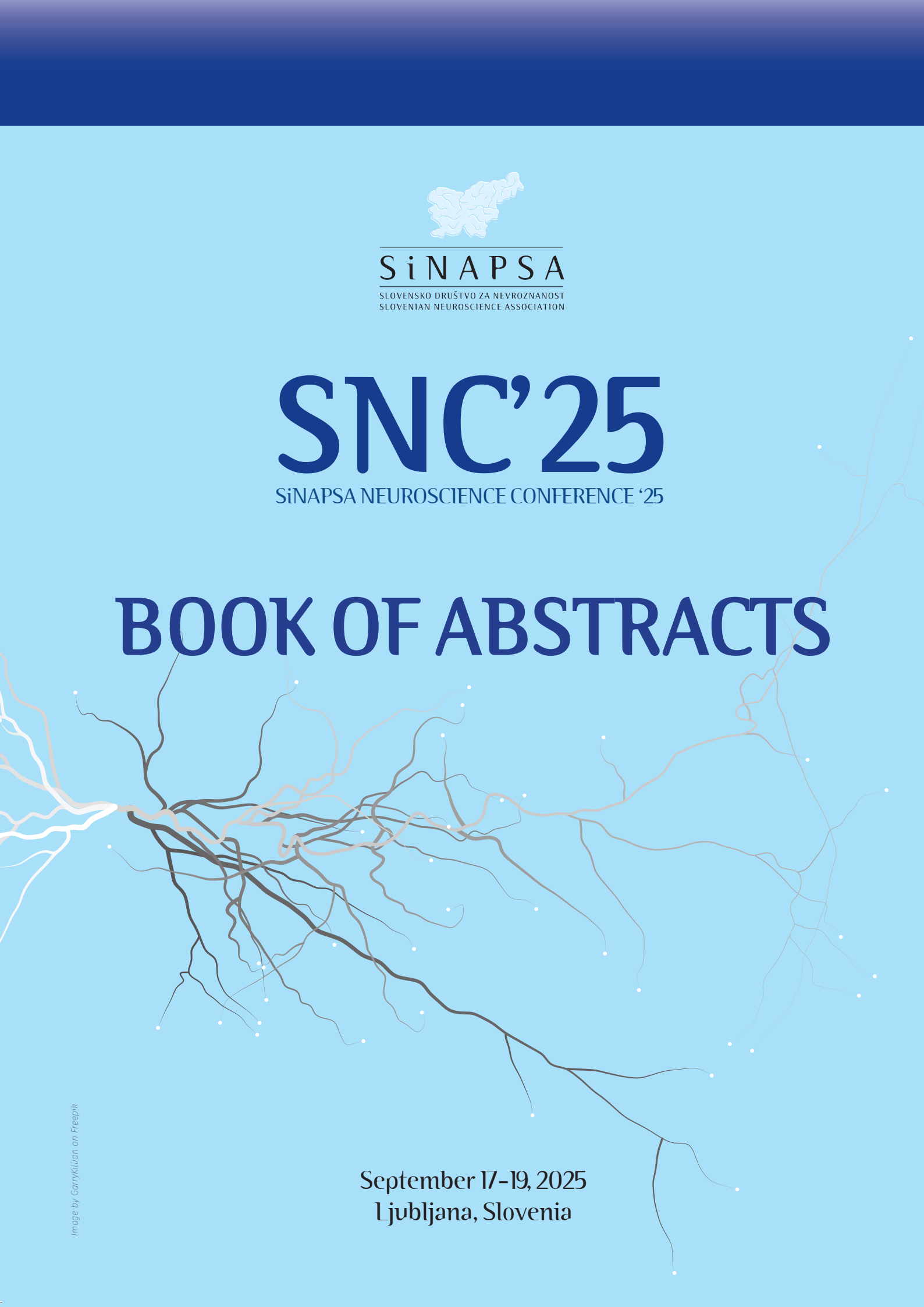
SiNAPSA

SLOVENSKO DRUŠTVO ZA NEVROZNANOST
SLOVENIAN NEUROSCIENCE ASSOCIATION

SNC'25

SiNAPSA NEUROSCIENCE CONFERENCE '25

BOOK OF ABSTRACTS



September 17–19, 2025
Ljubljana, Slovenia

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SiNAPSA Neuroscience Conference '25
Ljubljana, 17–19 September 2025

Organised by
SiNAPSA, Slovenian Neuroscience Association, Faculty of Medicine, University of Ljubljana, and Slovenian Society of Clinical Neurophysiology

SNC'25 Programme Committee
Boris Rogelj (Chair), Jure Bon, Emanuele Buratti, Blaž Koritnik, Helena Motaln, Matej Perovnik, Grega Repovš, Nina Omejc, Damjan Osredkar, Nina Vardjan, Jerneja Nimac

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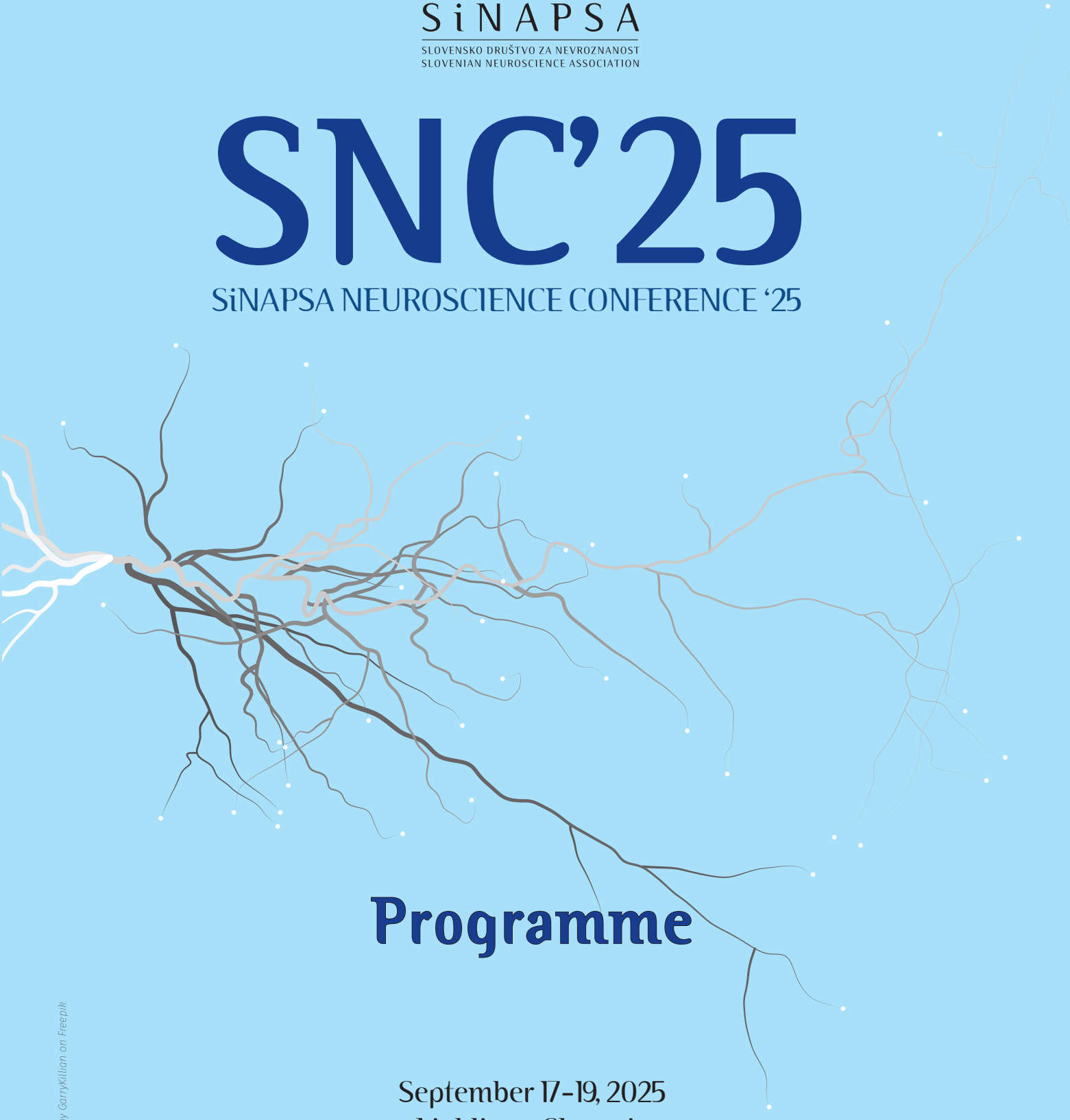
SNC'25

SiNAPSA NEUROSCIENCE CONFERENCE '25



Programme

September 17-19, 2025
Ljubljana, Slovenia

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SiNAPSA Neuroscience Conference ’25 Programme

Wednesday, 17 September 2025

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Vladimir Parpura

14:00—16:00 Symposium | Hall 1
Glia contribution to brain function in health and disease: from exocytosis and signaling to metabolism
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Making sense of glial adhesion GPCR biology
Nicole Scholz

Two tales of astrocyte pathology: Alzheimer disease and amyotrophic lateral sclerosis
Vedrana Montana

Dysregulation of octopaminergic Ca^{2+} signaling and metabolism in the aging *Drosophila* brain
Anemari Horvat

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Damjan Osredkar

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Thursday, 18 September 2025

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Novel proteins involved in the FUS-mediated biogenesis of sdRNAs in human cells
Patrycja Świergiel

Small RNAs regulate TDP-43 aggregation
Klementina Polanec

NTRK3 as a mediator of neuronal differentiation in sonic hedgehog pathway-activated medulloblastoma
Lea Erjavc

The miRNA 216b-5p acts as a tumor-suppressor by manipulating cell cycle progression in glioblastoma cells
Alexandra Lang

Heightened risk of tau pathology onset following SARS-CoV-2 infection
Vincenzo Iannone

Individual differences in global brain connectivity changes after rTMS for depression: an exploratory study
Jana Verdnik

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Precision therapeutics for amyotrophic lateral sclerosis
Oscar Wilkins

10:00—10:30 Coffee by the Posters | Poster exhibition area

10:30—11:15 Plenary talk | Hall 1
A little competition is a good thing: the friendly rivalry of Rho Guanine Nucleotide Exchange Factor (RGNEF) with TDP-43
Michael Strong

11:15—12:15 Biogen Satellite Symposium | Hall 1
Tofersen - new treatment for SOD1 ALS
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13:00—15:00 Symposium | Hall 1

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Chairs: Matej Perovnik, Maja Trošt

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Joachim Brumberg

Healthy and disease-specific metabolic brain networks in patients with neurodegenerative disorders

Matej Perovnik

Exploring connectivity patterns in dual phase PET imaging

Débora Elisa Peretti

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Tomaž Rus

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3D-cell and animal models

Chair: Helena Motaln

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Peter Ponsaerts

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Edor Kabashi

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Sergej Pirkmajer

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Elise van Breedam

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David Bartres Faz

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Chair: Jurij Bon

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Aleš Oblak

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Emanuele Buratti

FUS modulates the level of rRNA modifications and ribosome activity in health and disease

Dorota Raczyńska

RNA mechanisms associated with *C9orf72* mutation in ALS and FTD

Boris Rogelj

TDP-43 posttranslational modifications in stress

Jerneja Nimac

European Partnership for Brain Health (EP BrainHealth): advancing collaborative research, innovation and societal impact

David Krivec

20:00—23:00 Social event | Slamič Cafe

Friday, 19 September 2025

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Chair: Blaž Koritnik

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Andrea Calvo

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Francesca Palumbo

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Ana Kuder

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Trends and challenges in artificial intelligence
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Artificial intelligence in neurobiology
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Artificial intelligence and neuromuscular system
Aleš Holobar

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16:15—18:30 Educational Workshop | Hall 1
Artificial intelligence in neuroscience

Artificial intelligence in brain imaging
Blaž Škrlj

Artificial intelligence in clinical neurology
Dejan Georgiev

Artificial intelligence in psychiatric diagnostics
Jurij Bon

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Thursday, 18 September 2025

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Anja Suhadolc

CEL.03 The role of tenascin-C in the structural plasticity of perineuronal nets in the hippocampus
Ana Jakovljević

CEL.05 High extracellular K^+ triggers metabolic and morphological changes in brain cells
Nina Vardjan

CEL.07 L-lactate and GPR27 agonists modulate citrate production in 3T3 cells and astrocytes
Ena Sanjković

Clinical Neuroscience A

CLI.01 Coexisting subdural hematoma in cerebral amyloid angiopathy: a case series
Lara Straus

CLI.03 The miRNA 216b-5p acts as a tumor-suppressor by manipulating cell cycle progression in glioblastoma cells
Alexandra Lang

CLI.05 Does personalized TMS offer superior therapeutic outcomes compared to conventional TMS protocols in depression?
Albert Calsina-Latorre

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COG.01 CT-optimal touch modulations on somatosensory-motor integration and proprioception and the role of vision
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COG.03 High evening smartphone use drives sleep debt and lower morning affect in athletes
Liza Rozman

Computational Neuroscience A

COM.01 Exploring electroencephalographic (EEG) models of brain activity using automated modelling techniques
Nina Omejc

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MOL.01 Evaluation of nociception in a model of Parkinson's disease for the study of non-motor symptoms in TRPV4-/- animals
Leonardo Gomes Pereira

MOL.03 Novel proteins involved in the FUS-mediated biogenesis of sdRNAs in human cells
Patrycja Świergiel

MOL.05 Role of the FUS in rRNA modifications and ribosome activity in ALS model
Anna Bieluszewska

MOL.07 TDP-43 posttranslational modifications in stress
Jerneja Nimac

MOL.09 Study of the interaction between phenylalanine-tRNA synthetase (FARS) and *C9orf72* antisense RNA transcripts containing C_4G_2 hexanucleotide repeats
Tomaž Žagar

MOL.11 Non-genetic amino acid substitutions in proteins associated with the neurodegenerative diseases amyotrophic lateral sclerosis and frontotemporal dementia
Jure Pohleven

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Lenča Belehar

OTH.03 Too much of a good fat? Lasting behavioural impact of a maternal plant-based high-fat diet on emotional and exploratory behaviour in adult female offspring
Emilija Đurić

OTH.05 Comprehensive treatment of children and adolescents with special health care needs and disability (SEND)
Tina Bregant

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Kristian Elersič

Friday, 19 September 2025

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Urška Černe

CEL.06 Regulation of second messenger dynamics and mechanosensitivity in 3T3 cells and astrocytes by the orphan receptor GPR27
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Clinical Neuroscience B

CLI.02 Individual differences in global brain connectivity changes after rTMS for depression: an exploratory study
Jana Verdnik

CLI.04 The psychological situation of family caregivers of relatives with dementia
Maria Costa Neves

CLI.06 Twins with dystonic diparesis: is it CP or is it CTNNB1 mutation?
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COG.04 Subclinical anxiety is associated with reduced self-distancing and enhanced guilt-related connectivity between anterior temporal and subgenual cingulate cortex
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Molecular Neuroscience B

MOL.02 Heightened risk of tau pathology onset following SARS-CoV-2 infection
Vincenzo Iannone

MOL.04 NTRK3 as a mediator of neuronal differentiation in sonic hedgehog pathway-activated medulloblastoma
Lea Erjavc

MOL.06 Small RNAs regulate TDP-43 aggregation
Klementina Polanec

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Vera Župunski
MOL.10 Highly sensitive detection of cytoplasmic antisense *C9orf72* Repeat RNA via RNA–RNA proximity ligation assay
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Katarina Bobić
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Vesna Logonder
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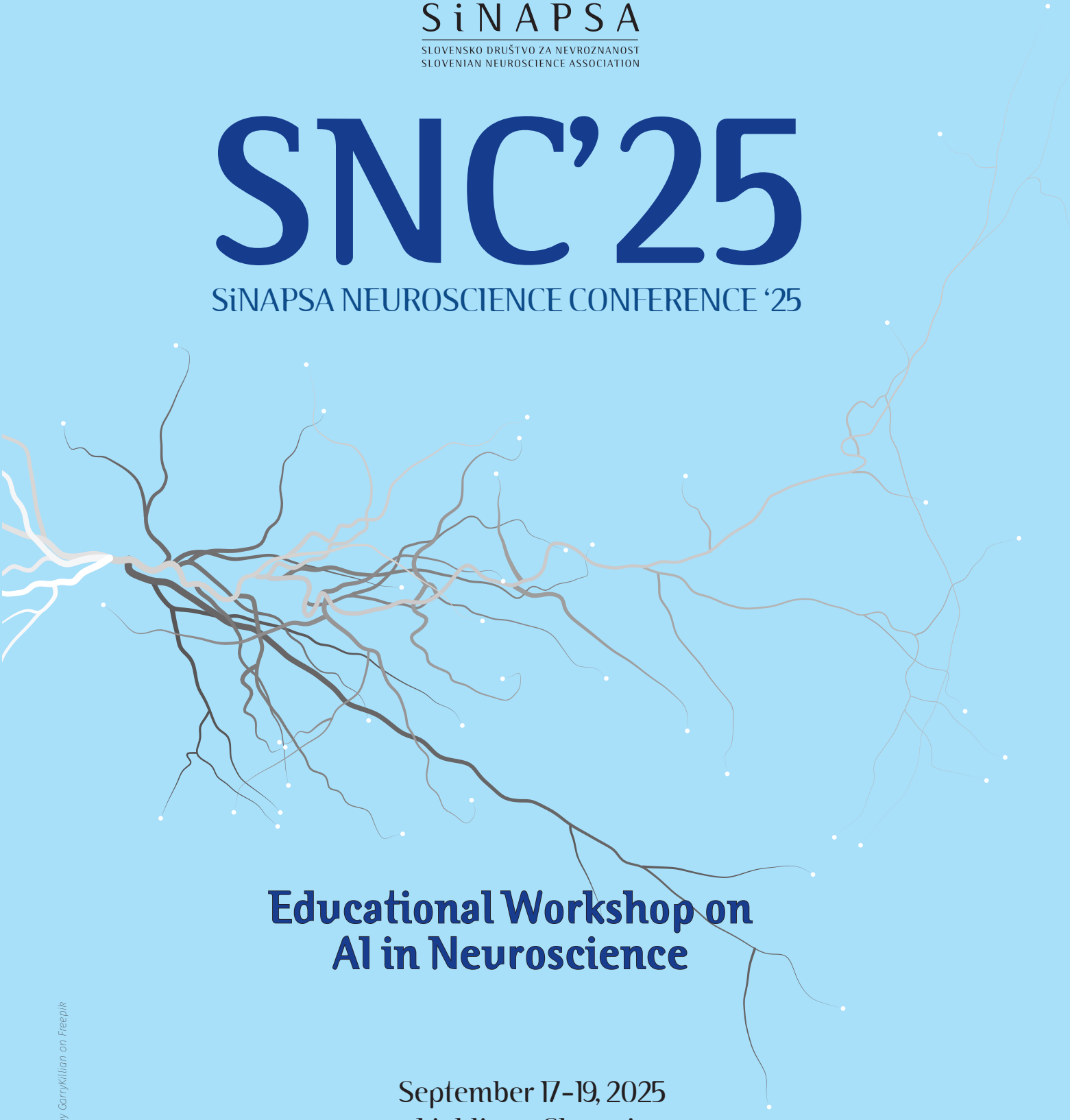

Educational Workshop on AI in Neuroscience

September 17-19, 2025
Ljubljana, Slovenia

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Trends and challenges in artificial intelligence
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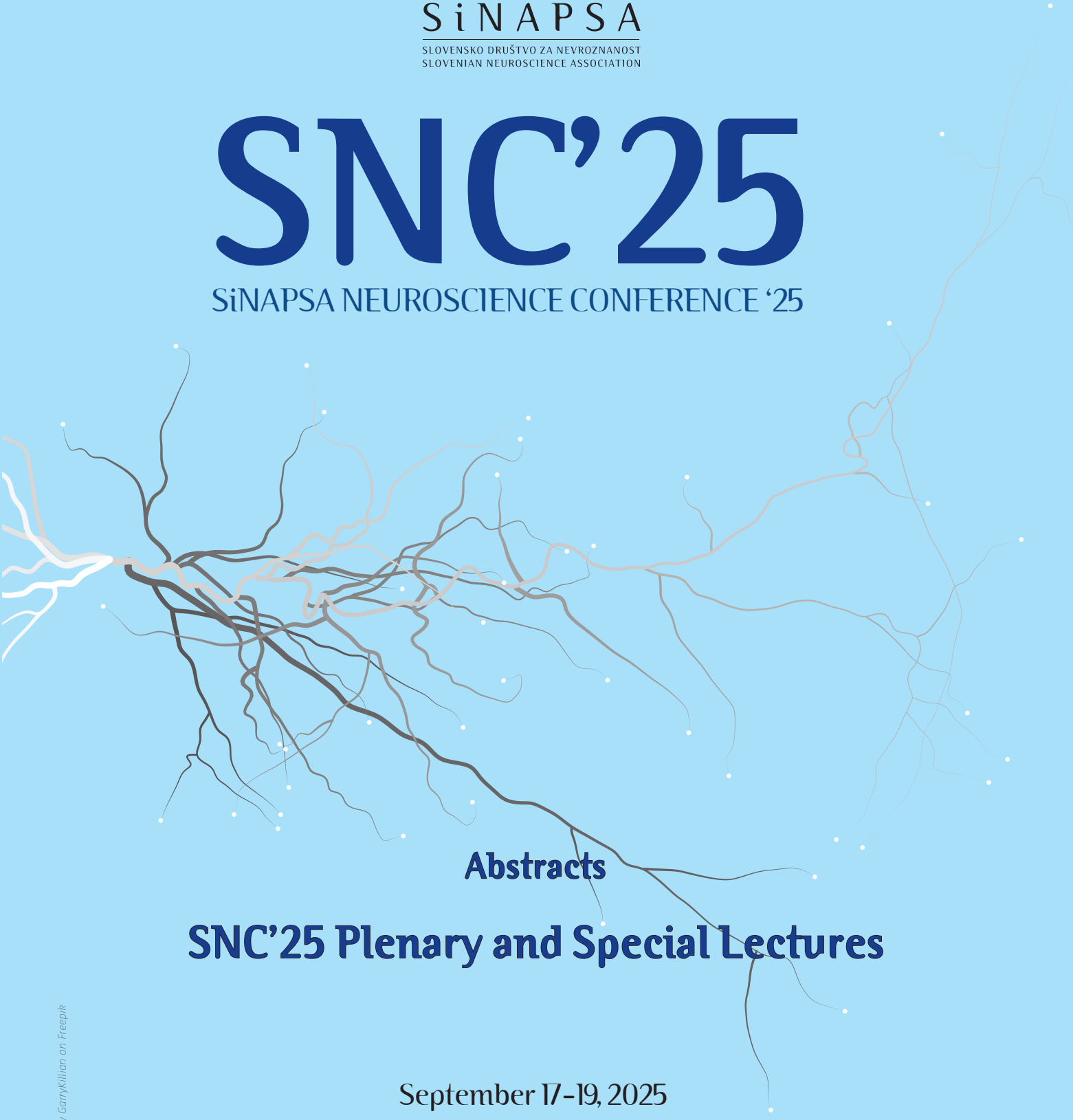

Abstracts

SNC'25 Plenary and Special Lectures

September 17-19, 2025
Ljubljana, Slovenia

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Wednesday, September 17th, 13:15

Astrocytes release glutamate by regulated exocytosis in health and malignancy

Vladimir Parpura

Zhejiang Chinese Medical University, Hangzhou, China

Parpura will present you with the evidence that astrocytes, a subtype of glial cells in the brain, can exocytotically release the neurotransmitter glutamate and how this release is regulated. Spatiotemporal characteristic of vesicular fusion that underlie glutamate release in astrocytes will be discussed. He will also present data on a translational project in which this release pathway can be targeted for the treatment of glioblastoma, the deadliest brain cancer.

Thursday, September 18th, 10:30

A little competition is a good thing: the friendly rivalry of Rho Guanine Nucleotide Exchange Factor (RGNEF) with TDP-43

Michael Strong

Departments of Clinical Neurological Sciences and Pathology & Laboratory Medicine, Robarts Research Institute, Western University, London, Ontario, Canada

Approximately 97% of both familial and sporadic variants of ALS demonstrate the neuropathological hallmark of alterations in metabolism of the DNA/RNA binding protein TDP-43. Under physiological conditions, TDP-43 can function as a stress response protein, undergoing a nucleocytosolic redistribution and incorporation into biomolecular condensates through a process of liquid-liquid phase separation. Under pathological conditions, this process progresses through liquid-solid phase separation (LSPS) into increasingly dense hydrogels with limited diffusibility, forming pathognomic intraneuronal fibrils and condensates. The challenge is that this apparently linear progression belies a fundamental alteration in RNA biogenesis, including perturbations in the expression of a broad array of small RNAs, including miRNA, lncRNAs and circRNAs, alterations in splicing and the expression of cryptic exons. Consistent with the postulate that ALS is a broadly-based disorder of RNA metabolism, such condensates incorporate a number of ALS-associated RNA binding proteins as polymeric structures, including Rho Guanine Nucleotide Exchange Factor (RGNEF). We recently reported that a N-terminal fragment of RGNEF (NF242) can prevent the induction of neuronal degeneration when co-expressed with TDP-43^{WT} in *drosophila melanogaster,* resulting in normal lifespan and motor function. Intriguingly, intraneuronal condensates of TDP-43 colocalizing with NF242 persisted, suggesting that a return to physiological homeostasis did not require dissolution of the condensates. A similar phenomenon of extending lifespan while TDP-43 condensates persist was observed in studies using the rNLS8 double transgenic C57Bl/6 mouse (NEFH-tTA$^{+/-}$ / tetO-hTDP-43$^{\Delta NLS}$) in which we administered self-complementary adeno-associated viruses (AAVs) serotype 9 expressing NF242 (AAV9/NF242). We have shown that NF242 interacts directly with the RNA binding domain of TDP-43, and that this interaction is dependant on its IPT/TIG domain. Distinct from this physicochemical interaction, however, RGNEF acts to counteract several functions of TDP-43 that include impacts on NEFL mRNA stability, RNA expression and exon skipping/inclusion. These observations raise the intriguing possibility that the restoration of aspects of RNA homeostasis by RGNEF can occur independent of dissolution of pathological condensates.

Research supported by the Temerty Family Foundation and the Canadian Institutes of Health Research

Late breaking news
Thursday, September 18th, 9:40

Precision therapeutics for amyotrophic lateral sclerosis

Oscar Wilkins

Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, University College London, United Kingdom
The Francis Crick Institute, London, United Kingdom

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is a devastating neurodegenerative disease with no effective treatments. However, despite disease heterogeneity at both the genetic and symptomatic levels, 97% of cases are unified by a central disease mechanism: TDP-43 pathology. TDP-43 pathology leads to both a loss of proteostasis and alterations in splicing regulation. Here, I will present our work on ameliorating TDP-43 pathology, via both antisense oligonucleotides and gene therapies. I will focus on two novel precision gene therapy approaches that we have recently developed, which target TDP-43 pathology while simultaneously exploiting this disease mechanism to improve precision.

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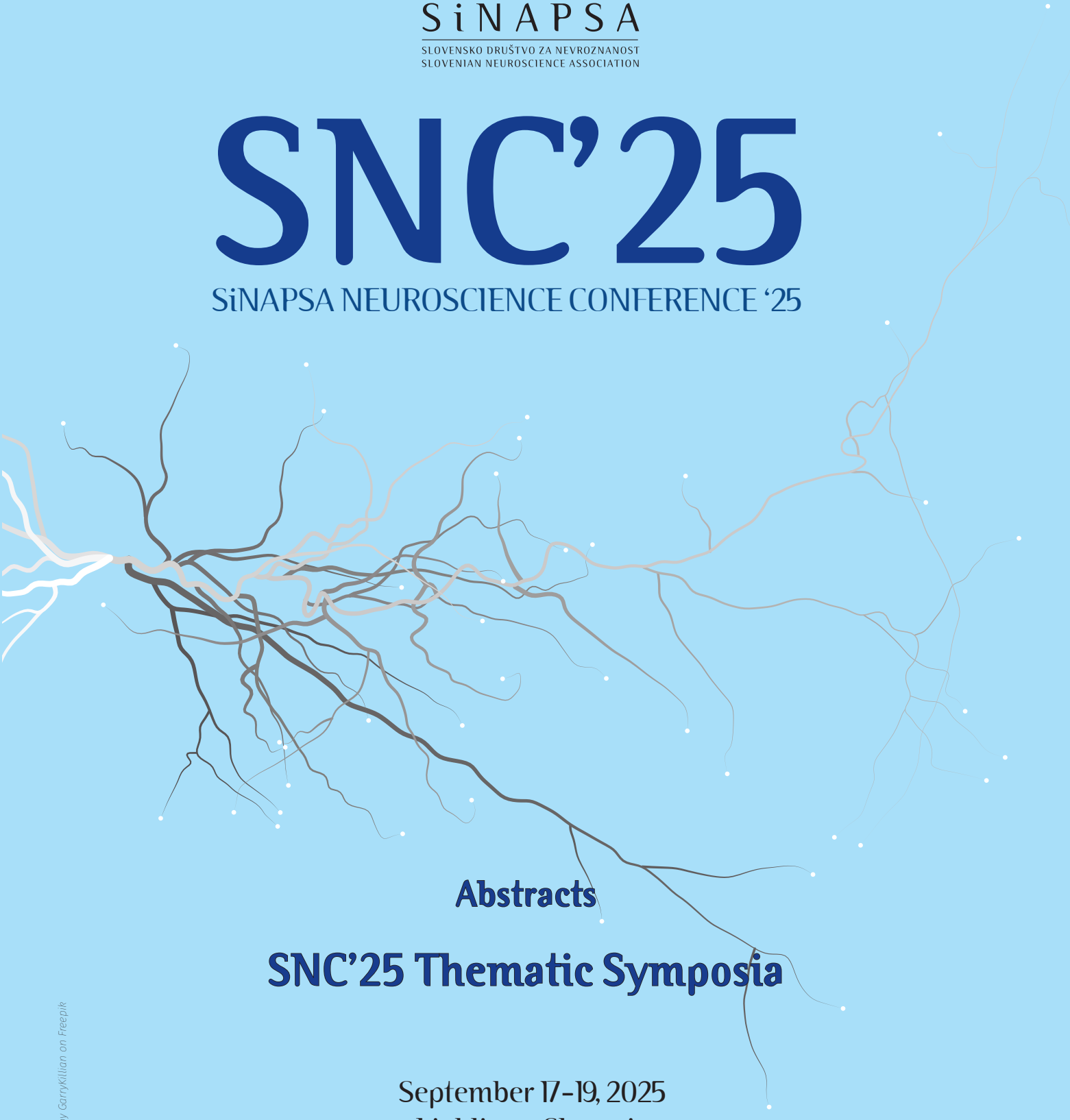

Abstracts

SNC'25 Thematic Symposia

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Ljubljana, Slovenia

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Wednesday, September 17th, 14:00

Glia contribution to brain function in health and disease: from exocytosis and signaling to metabolism

Making sense of glial adhesion GPCR biology

Lara-Sophie Brodmerkel[1], Anne Bormann[1], Anemari Horvat[2,3], Stefanie Schirmeier[4], Nina Vardjan[2,3], Dmitrij Ljaschenko[1], Nicole Scholz[1]

1 Rudolf Schönheimer Institute of Biochemistry, Division of General Biochemistry, Medical Faculty, Leipzig University, Germany
2 Laboratory of Neuroendocrinology − Molecular Cell Physiology, Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, Slovenia
3 Laboratory of Cell Engineering, Celica Biomedical, Ljubljana, Slovenia
4 Faculty of Biology, Technische Universität Dresden, Germany

Adhesion G protein-coupled receptors (aGPCRs) are a structurally and functionally distinct GPCR family distinguished by large extracellular domains that mediate cell–cell and cell–matrix interactions. By virtue of this architecture, aGPCRs are ideally equipped to integrate both chemical and mechanical cues, yet the molecular mechanisms underpinning their function remain often poorly defined. Here, we focus on the ancient aGPCR ADGRL/Cirl—the *Drosophila* homolog of Latrophilin – together with its interactor, Toll-like receptor 8, to dissect the molecular pathways that govern aGPCR-dependent signaling within glial cells and across glia–neuron junctions. As pharmacologically accessible targets, elucidating aGPCR's glia-specific roles may open new therapeutic avenues for modulating glial function in neurological and neurodegenerative disease contexts.

Funding: This work was supported by grants from the Deutsche Forschungsgemeinschaft to N.S. (CRC 1423 project number 421152132, subproject B06)

Two tales of astrocyte pathology: Alzheimer disease and amyotrophic lateral sclerosis

Vedrana Montana

International Translational Neuroscience Research Institute, Zhejiang Chinese Medical University, Hangzhou, P.R. China

Astrocytes play an important role in maintaining brain homeostasis being that regulating metabolism, cleaning excess of neurotransmitters, preserving ion balance or modulating activities by gliotransmission, such as Ca^{2+}-dependent exocytotic release of glutamate. Chronic failure in maintaining homeostasis in the brain has been an underlining cause of many neurodegenerative illnesses, and astrocytes have prominent role in them.

Astrocytes are implicated to have a central role in the cellular phase of Alzheimer Disease, AD, as they are responsible for maintaining connectivity by releasing gliotransmitters. Presenilins, known of its γ-secretase activity, also function as leak Ca^{2+}-channels in the ER membrane. Mutations of presenilins disturb Ca^{2+} permeability and, consequently, intracellular Ca^{2+} dynamics. Although astrocytes express both forms of presenilin, the role of their mutated forms on Ca^{2+} homeostasis, Ca^{2+} dynamics or Ca^{2+}-dependent glutamate release has not been extensively studied. Data suggest that changes in the processes could have profound impact in early stages and progression of AD.

Amyotrophic Lateral Sclerosis, ALS, is a fatal neurodegenerative disease that affects nerve cells in the brain and spinal cord leading to muscle weakness, twitching, and atrophy. Astrocytes in ALS can become dysfunctional, changing their shape, molecular expression patterns and function, contributing to pathology at many different levels such are mitochondrial dysfunction, oxidative stress, energy metabolism impairment, protein misfolding, or glutamate excitotoxicity. These changes can lead to astrocyte-mediated neurotoxicity. Data imply that alterations in calcium dynamics and exocytotic glutamate release in astrocytes of ALS patients are contributing factor in glutamate excitotoxicity and disease progression.

Dysregulation of octopaminergic Ca^{2+} signaling and metabolism in the aging *Drosophila* brain

Anemari Horvat[1,2], Urška Černe[1], Anne-Kristin Dahse[3], Robert Zorec[1,2], Nicole Scholz[3], Nina Vardjan[1,2]

1 Laboratory of Neuroendocrinology − Molecular Cell Physiology, Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, Slovenia
2 Laboratory of Cell Engineering, Celica Biomedical, Ljubljana, Slovenia
3 Division of General Biochemistry, Rudolf Schönheimer Institute of Biochemistry, Medical Faculty, Leipzig University, Leipzig, Germany

Aging impairs nervous system function, causing cognitive and motor decline. This may be associated with altered brain metabolism and signaling, potentially driven by noradrenergic system dysfunction, regulating metabolism and behavior. Noradrenaline activates adrenoceptors on brain cells, triggering cytosolic Ca^{2+} and cAMP signaling. In astrocytes, this facilitates glucose uptake, glycogen degradation, and lactate production via aerobic glycolysis. Lactate can be transported to neurons and used as fuel supporting heightened brain activity, essential for learning and memory formation. Whether aging impairs noradrenergic regulation of brain cell metabolism, contributing to behavioral dysfunction, remains unclear.

To investigate this, we used fluorescent sensors to monitor Ca^{2+}, cAMP, glucose and lactate in neurons or glia in response to octopamine (an invertebrate noradrenaline analogue) in young and aged *Drosophila* brains. Aging in *Drosophila* was associated with neurodegenerative brain lesions, reduced locomotion and altered whole-brain metabolism. Octopamine-induced Ca^{2+} increases in neurons and glia were absent in aged brains, suggesting impaired Ca^{2+} signaling, possibly due to altered octopamine/tyramine receptor expression, as suggested by observed Tyr1 receptor downregulation. In contrast, octopamine-induced increases in cAMP and lactate were unaffected by aging and more pronounced in neurons, suggesting that aerobic glycolysis occurs predominantly in neurons. Only astrocytes exhibited octopamine-mediated increases in glucose, which were absent in aged brains. neuronal glucose uptake was reduced with age.

Our results suggest that neurons, not glia, are the primary site of regulated aerobic glycolysis in *Drosophila* brains. In aged brains, the observed impaired octopaminergic Ca^{2+} signaling, glial glucose uptake and its delivery to neurons may contribute to age-related behavioral dysfunction.

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Cannabinoid and noradrenergic regulation of glycogen-derived lactate production in astrocytes

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Astrocytes play a vital role in brain energy metabolism and neurotransmission, serving as both structural and metabolic intermediaries between neurons and blood vessels. These glial cells facilitate glucose uptake and store it as glycogen, serving as an energy reserve that can be rapidly mobilized during neuronal activation. Noradrenaline (NA) induces L-lactate production in astrocytes via a mechanism that necessitates D-glucose uptake and its transit through the glycogen shunt. Our results show that, under adrenergic stimulation, most D-glucose utilized by astrocytes enters glycolysis only after temporary incorporation into glycogen, highlighting the importance of glycogen turnover in supporting astrocytic metabolism. Based on these findings, our study explores the additional modulatory role of the endocannabinoid system (eCS) in astrocyte energy metabolism. The eCS, consisting of CB1 and CB2 receptors and their lipid-derived ligands, is increasingly recognized for its regulatory influence in the central nervous system. We assessed how cannabinoid signaling affects astrocytic metabolic pathways, specifically intracellular glucose and lactate levels, calcium dynamics, and glycogen utilization. Using primary cultured rat astrocytes, we applied genetically encoded FRET-based nanosensors (Laconic and FLII12Pglu-700μδ6) to monitor real-time changes in cytosolic L-lactate and D-glucose. Pharmacological activation of CB1 and CB2 receptors significantly elevated both metabolites, indicating enhanced aerobic glycolysis. Notably, CB2 receptor activation triggered a more robust metabolic response than CB1, accompanied by a pronounced depletion of glycogen stores. This suggests that CB2 signaling engages glycogenolytic pathways, paralleling the effects observed with noradrenaline but possibly involving distinct intracellular signaling cascades. To delineate the mechanisms behind these effects, we employed selective inhibitors: 2-deoxy-D-glucose (2-DG) to block glycolysis, DAB to inhibit glycogenolysis, and 3-nitropropionic acid (3-NPA) to inhibit oxidative phosphorylation. Our results confirm that noradrenaline-induced lactate production relies exclusively on glycogen-derived glucose, even in the presence of extracellular D-glucose. Together, our findings suggest integration of the eCS as a parallel regulatory axis in astrocyte metabolism. The CB2 receptor emerges as a potent modulator of glycogen turnover and lactate production.

Amisyn is required for β-adrenergic inhibition of MHC-II surface expression and fusion pore conductance decrease in astrocytes

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Neurodegeneration is initiated by the decay of the noradrenergic nucleus locus coeruleus, leading to reduced bioavailability of noradrenaline (NA), enhancing neuroinflammation through reactive astrocytes, but the mechanism(s) are unclear. We studied whether interferon-γ-triggered expression of major histocompatibility complex class II (MHC-II) molecules, a hallmark of reactive astrocyte proinflammatory status, is regulated by adrenergic receptors, and amisyn, a regulator of exocytosis. The results revealed that β-, but not α-adrenergic treatment, increasing cAMP, reduced immunocytochemically detected MHC-II expression in rat astrocytes; β-adrenergic treatment inhibited transient exocytosis of lysosome-like vesicles, monitored by membrane capacitance recording, increased the frequency of transient exocytotic events, but reduced fusion-pore conductance and dwell-time, impeding MHC-II surface expression. Overexpressed wild-type amisyn inhibited surface expression of MHC-II and CD63, a lysosomal marker, and decreased fusion-pore conductance and fusion-pore dwell-time. Conversely, reduced amisyn expression enhanced exocytosis of larger vesicles, increased fusion-pore conductance and dwell-time, but abolished β-adrenergic effects. Amisyn mediates β-adrenergic inhibition of exocytosis and MHC-II expression.

Wednesday, September 17th, 16:30

CTNNB1 neurodevelopmental syndrome: from dreams to novel treatment options

New frontiers in rare diseases

Damjan Osredkar

Department of Pediatric Neurology, University Children's Hospital, University Medical Centre Ljubljana, Slovenia

Rare diseases are a group of heterogeneous and often life-threatening disorders characterized by low prevalence, diagnostic complexity and limited treatment options. Advances in molecular biology, genetics and drug development over the last decade have profoundly changed the management of many of these conditions, including in Slovenia. Spinal muscular atrophy (SMA) is one of the first rare inherited neuromuscular diseases for which new targeted and gene therapies have markedly improved clinical outcomes and prognosis. Similar opportunities for targeted approaches are emerging in other neurological disorders with a genetic basis, such as cerebral palsy. A particular example is CTNNB1 neurodevelopmental syndrome, for which in Slovenia—through collaboration between parents, clinicians and researchers at home and abroad—we have developed a home-grown candidate gene therapy. Such breakthroughs demonstrate that, through interdisciplinary work and international collaboration, meaningful advances can be achieved even for diseases for which no treatments yet exist. Nevertheless, numerous challenges remain, from long-term safety to high costs and ethical questions. Open dialogue among patients, professionals and the public is essential to ensure that new therapies are accessible, safe and accepted. With its professional and research capacities, Slovenia has the opportunity to rank among the leading countries in innovative treatment of rare diseases.

The past, presence, and future of vector-based gene therapies: how technological advancements help us maximising clinical impact and benefits to the patients

Leszek Lisowski

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Gene2Cure Foundation, USA

Gene therapy, the therapeutic use of genes as medicines, holds immense promise for delivering clinical benefits to millions of children affected by currently incurable genetic disorders. After decades of limited progress and disappointing outcomes, the technology underlying viral vector–based gene therapies has now reached a level of maturity that enables the development of safe and effective treatments. Among these, adeno-associated virus (AAV)–derived vectors have emerged as the leading platform for gene transfer in translational virology. Indeed, seven AAV-based therapies have already received regulatory approval, with hundreds more currently progressing through various stages of clinical development.

Despite these landmark achievements, clinical data from hundreds of phase I/II/III AAV-based trials clearly demonstrate that current-generation recombinant AAV (rAAV) vectors remain inefficient at transducing human cells. Consequently, for AAV-based therapies to fully realise their transformative potential, novel vectors preselected on human target tissues must be developed.

In his presentation, Prof. Lisowski will provide an overview of rAAV vectorology and state-of-the-art vector selection strategies designed to identify novel variants with clinically relevant properties. The presentation will highlight how different selection systems and methodologies influence the functional characteristics of candidate vectors. Beyond the technological perspective, Prof. Lisowski will describe how his team leverages advanced gene transfer technologies and the dedicated infrastructure he has helped establish in Australia to develop therapies for rare and ultra-rare genetic conditions, including CTNNB1 syndrome. The talk will also address the unique scientific, translational, and healthcare challenges associated with gene therapies for rare diseases, and will consider how ongoing technological innovation and evolving regulatory frameworks can help ensure equitable access to these potentially life-changing treatments for all patients, regardless of geographic location or socioeconomic status.

Design and *in vitro* validation of an AAV-mediated gene therapy for CTNNB1 syndrome

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CTNNB1 Syndrome is a rare neurodevelopmental disorder caused by mutations in the *CTNNB1* gene, which impair the production and function of the β-catenin protein—essential for brain development, synapse formation, and neuronal maturation.

As a result, around 97% of affected individuals experience developmental delays. While no treatment currently exists, the monogenic nature of the disorder makes it a promising candidate for gene therapy. Gene therapy involves introducing exogenous genetic material into target cells to correct or compensate for defective genes. Among the various delivery systems available, adeno-associated viruses (AAVs) have emerged as the vector of choice due to their favourable safety profile. AAVs are non-pathogenic to humans, exhibit low immunogenicity, and enable long-term persistence of the therapeutic gene as an episome, making them particularly suitable for treating monogenic disorders.

We have designed a therapeutic approach based on recombinant AAV vectors to deliver a functional copy of the *CTNNB1* gene and restore β-catenin expression. During the talk, we will discuss in vitro studies which demonstrate that this strategy successfully restored β-catenin expression and function in preclinical models of CTNNB1 Syndrome. Encouraging functional data and favourable safety profile position our AAV-CTNNB1 augmentation strategy as a promising avenue towards an experimental therapy for this devastating and today incurable condition.

Determination of efficacy, safety and toxicity for CTNNB1 syndrome gene therapy *in vivo*

Duško Lainšček[1,2], Andrea Perez-Iturralde[3], Damjan Osredkar[4,5], Ruud Bueters[6], Jan Prochazka[7], Radislav Sedláček[7], Eva Štefancová[7], Šárka Suchanová[7], José L. Lanciego[8], Leszek Lisowski[3], Špela Miroševič[9,10]

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8 Department of Neurosciences, Center for Applied Medical Research (CIMA), University of Navarra, Pamplona, Spain
9 CTNNB1 Foundation, The Gene Therapy Research Institute, Ljubljana, Slovenia
10 Department for Family Medicine, Faculty of Medicine, University of Ljubljana, Slovenia

Preclinical animal testing of gene therapies is a critical step to ensure safety and efficacy before advancing to human trials. These studies evaluate potential risks, identify adverse effects, and determine safe dosage levels, thereby facilitating the development of effective and safe therapeutic strategies. In the context of developing AAV9-based gene therapy for CTNNB1 Syndrome, heterozygous *Ctnnb1* mouse model was developed and characterized. Intracerebroventricular injections of the therapeutic vector demonstrated significant increases in CTNNB1 transgene and β-catenin protein levels within the brain, with behavioral and motor assessments confirming amelioration of disease phenotype. Safety analyses, including tissue-level DNA and protein evaluations, blood biochemistry, and histopathology, indicated no adverse effects on peripheral organs such as the liver, and comprehensive *in vivo* studies supported the therapy's safety profile. Next, extensive GLP-compliant toxicity and biodistribution assessments were conducted using mouse and non-human primate models, where Urbagen, an AAV9-based therapy, was administered via intracerebroventricular injection. These studies showed no significant systemic toxicity or treatment-related effects, with only expected microscopic lesions at high doses, consistent with known AAV9 neuronal influences. Overall, the preclinical data demonstrate that the Urbagen gene therapy approach is safe and effective, supporting the progression toward clinical trial for the CTNNB1 Syndrome patients.

Development of gene replacement therapy for CTNNB1 syndrome: funding, coordinating and the parental experience

Špela Miroševič

CTNNB1 Foundation, The Gene Therapy Research Institute, Ljubljana, Slovenia

CTNNB1 syndrome is a rare and severe neurodevelopmental disorder first described in 2012. Since then, more than 500 families worldwide have connected through social media groups and patient organizations. With the limited industry interest, in rare and ultra-rare conditions, families and patient-led groups often become the main funders and drivers of therapeutic development. The CTNNB1 Foundation, The Gene Therapy Research Institute, was established in 2021 following the diagnosis of a Slovenian child with CTNNB1 syndrome. The foundation was created to raise funds, connect researchers and clinicians, and advance gene therapy toward clinical trial. Since its founding, the organization has coordinated preclinical development including efficacy and safety testings in different animal models, as well as manufacturing and regulatory preparation and submission through the Clinical Trial Information System (CTIS). Throughout the years, collaboration with the medical team at the Pediatric hospital Ljubljana has been critical in the whole clinical development, including preparing first clinical trial. Given limited commercial investment, funding relied on combining philanthropy, community initiatives, and public support. More than 4 million euros was raised through families and communities worldwide, complemented by a 1 million euros national contribution from Slovenia after a legislative change and early commitments from Brazil to support patient access. These resources enabled completion of manufacturing, key preclinical milestones, and preparation for a clinical trial. This presentation illustrates how a patient-led foundation can coordinate a cross-border therapeutic program. It outlines the funding strategy, governance, and scientific collaborations, and also integrates the parental perspective: balancing caregiving with research leadership, the importance of transparency and trust, and lessons that may inform other ultra-rare disease communities across Europe and beyond.

Thursday, September 18th, 13:00

3D-cell and animal models

From stem cells to smart brains in the lab

Peter Ponsaerts

Laboratory of Experimental Hematology, Vaccine and Infectious Disease Institute, University of Antwerp, Wilrijk, Belgium

Lab grown mini-brains encompass a large collection of *in vitro* stem cell-derived three-dimensional culture systems that aim to recapitulate multiple aspects of *in vivo* brain development and function. Our laboratory focusses on the functional characterisation of murine and human induced pluripotent stem cell (iPSC)-derived mini-brains in terms of immune competence and electrophysiological activity. The first part of the lecture will discuss our recent developments in the application of transcriptome-proteome integration analysis to study and modulate detrimental immune responses in microglia-containing murine iPSC-derived mini-brains. The second part of the lecture will discuss the influence of a stroke-like event and a viral infection on electrophysiological network activity in human iPSC-derived mini-brains. Providing these examples of ongoing research, we wish to contribute to a new research era using functionally competent human lab-grown mini-brains.

Advances in zebrafish models of ALS and related neurological diseases

Edor Kabashi

Institute IMAGINE – INSERM, Paris, France

Advances in genetic technologies have empowered the usage of zebrafish as an animal model, including for ALS (Amyotrophic Lateral Sclerosis) and related neurological diseases. Our team has targeted and developed mutants for the majority of zebrafish orthogues for ALS genetic factors, including C9orf72, TDP-43, FUS, p62 and TBK1. These vertebrate models have been quite useful to demonstrate the importance of these genes in motor neuron development and swimming abilities. Also, through unbiased approaches, including omics analysis, we demonstrate a number of key ALS pathways that are altered in these models, namely autophagy and metabolic pathways. Finally, I will also demonstrate some key parameters that are used to test therapeutic avenues in these models and their translatability potential.

De novo innervation of human myotubes as an experimental model to study development and function of human skeletal muscle *in vitro*

Sergej Pirkmajer, Katarina Miš, Tomaž Marš

Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, Slovenia

Cultured human skeletal muscle cells are frequently used to study various aspects of the physiology, pathophysiology, and pharmacology of human skeletal muscle *in vitro*. Most commonly, these cells are used either as proliferating myoblasts or as differentiated myotubes without neurons, depending on the purpose of the study. Another approach is the co-culture of human myotubes with explants of embryonic rat spinal cord, resulting in de novo innervation by motor neurons, the formation of well-structured neuromuscular junctions (NMJs), and further morphological and functional maturation of the myotubes. In contrast to aneurally cultured human myotubes, which normally do not contract when not electrically stimulated, the de novo innervated myotubes contract due to stimulation by motor neurons via the NMJs. This heterologous rat-human co-culture model not only enables experiments on highly developed contracting human myotubes, but is also useful because species-specific antibodies and gene expression assays can be used to study nerve-derived (i.e. rat) and muscle-derived (i.e. human) NMJ components under controlled *in vitro* conditions. Furthermore, by comparing gene expression in aneurally and innervated myotubes, the effects of innervation and contraction on the acquisition of functional properties of myogenic cells during myogenesis can be determined.

Induction of alpha-synuclein pathology in human iPSC-derived neurospheroids to model synucleinopathies

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Synucleinopathies are a group of neurodegenerative disorders characterized by the abnormal accumulation of misfolded alpha-synuclein (αSyn) protein in the brain. While significant insights have been gained so far into the aggregation, prion-like transmission, and toxicity of αSyn fibrils, most of these findings stem from animal models and traditional 2D in vitro cultures. To enable the study of αSyn pathology in a more human brain-like environment, we evaluated different strategies for inducing αSyn pathology in human iPSC-derived neurospheroids. Hereto, five month-old human iPSC-derived neurospheroids, composed of both neurons and astrocytes, were exposed to three conditions: (i) AAV-mediated overexpression of wild-type αSyn, (ii) addition of pre-formed αSyn fibrils (PFFs), or (iii) a combination of both, and were analysed by immunocytochemistry after 1 week, 1, 2 and 3 months. Immunostainings for αSyn, phosphorylated αSyn (p-αSyn) and thioflavin S were performed to evaluate αSyn overexpression, fibril uptake and the formation of pathological inclusions. Immunostaining for αSyn antigen confirmed successful αSyn overexpression in the AAV-transduced group and demonstrated fibril uptake by

the outer cell layers of the neurospheroids in the PFF-treated groups. Staining for p-αSyn, a marker of pathological αSyn accumulation, revealed induction of αSyn pathology in the PFF-treated conditions, with accelerated spread and accumulation observed when PFFs were combined with αSyn overexpression. Thioflavin S staining to detect β-sheet-rich structures characteristic of pathological inclusions further confirmed these findings. In conclusion, the addition of PFFs to five month-old human iPSC-derived neurospheroids, with or without AAV-mediated αSyn overexpression, proved to be the most effective in inducing widespread pathological changes, resembling those seen in human synucleinopathies. Further transcriptomic and proteomic analyses will now have to confirm that neurospheroids treated with PFFs represent a promising and physiologically relevant platform for studying αSyn pathology and potential therapies in a human brain-like context.

FUS phosphorylation in neurogenesis and neuromuscular junction formation

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Protein aggregation in neurons, which leads to the degeneration of axons and neuromuscular junctions (NMJ), is an early feature of neurodegenerative diseases. FUS (Fused in sarcoma) is a predominantly nuclear RNA-binding protein that mislocalizes to the cytoplasm in these diseases, where it aggregates. Under normal conditions, only a small amount of FUS is present in the cytoplasm, where it functions as an mRNA transporter to the distal neuronal sites where local protein translation is required. Since phosphorylation of the C-terminal tyrosine of FUS inhibits its binding to the nuclear importer transportin 1, allowing FUS to remain in the cytoplasm, we hypothesized that phosphorylated $FUS^{p\text{-}Y526}$ may be observed during neuronal cell differentiation and NMJ formation when distal translation is most active. The activity of Src family kinases is increased during embryonic development, is later downregulated and abnormally increased again during neurodegeneration. We have shown that c-Src, c-Abl and c-Fyn all phosphorylate FUS at Y526. Our aim was therefore to investigate the localization pattern of $FUS^{p\text{-}Y526}$ during neurogenesis using mouse and human neurospheroids and co-cultures of human myotubes innervated by neurons from embryonic rat spinal cord explants. By immunocytochemical staining, we showed that $FUS^{p\text{-}Y526}$ is present in the differentiating neurons and astrocytes of the neurospheroids. In the co-culture model, $FUS^{p\text{-}Y526}$ was preferentially observed in maturing axons and at the motor plates of the NMJ. Overall, this suggests an active role of $FUS^{p\text{-}Y526}$ during neuronal differentiation and NMJ formation, which could be perturbed by aberrant kinase activity and the consequent transition from FUS to $FUS^{p\text{-}Y526}$ during neurodegeneration. Deciphering the mechanisms underlying the normal and aberrant transition of FUS to $FUS^{p\text{-}Y526}$ could lead to new strategies for the treatment of neuromuscular disorders.

Noradrenergic regulation in brain: increased L-lactate in cortical astrocytes and locus coeruleus neurons

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Introduction: Astrocytes and neurons are metabolically coupled. According to the astrocyte-to-neuron lactate shuttle (ANLS) hypothesis, astrocytes produce L-lactate (LL), the end product of aerobic glycolysis (AG), which is then transported to neurons through monocarboxylate transporters located in the plasma membranes of both cell types. In neurons, LL is converted to pyruvate and used for energy production. In astrocytes, AG is potently activated by noradrenaline (NA), which is released mainly from neurons of locus coeruleus (LCn). LCn themselves express adrenergic receptors, particularly α_2, but also α_1 and β_2, pointing to a possible self-regulatory loop through which NA could also affect changes in intracellular LL in LCn. While astrocyte responses to NA depend on LCn activity and the number and types of NA receptors, which are regulated by several factors, including the interplay between different cell types as well as temperature fluctuations, but both remain poorly understood.

Aims: We investigated NA-stimulated intracellular LL dynamics and compared responses in astrocytes and LCn. We hypothesised that NA evokes specific LL transients in LCn, modulated by temperature and the presence of astrocytes through changes in NA receptor expression. Thus, the second aim was to determine the effects of temperature and the presence of other cells on noradrenergic receptor expression in LCn.
Methods: Primary neuronal and astrocytic cultures or co-cultures were prepared from 1-3 days old rat pups. Primary LCn cultures were kept at 37°C or 34°C (4 days prior to experiments) and co-cultures were kept at 37°C. Expression of α_{1A} and β_2 receptors was assessed by immunocytochemistry. Cells were transduced with genetically encoded FRET sensor *Laconic* using an adeno-associated viral vector. Fluorescence and intracellular LL dynamics were observed using confocal microscopy.

Results: In both LCn and astrocytes, stimulation with NA [100 μM] induced significant intracellular LL increases, with greater cumulative changes observed in LCn. The rates of LL changes were comparable between the cell types. Our data show that in LCn cultured at 34°C, β_2 expression is significantly increased, while α_{1A} levels remained unchanged. In LCn co-cultured with astrocytes, the intensity of α_{1A} signal was significantly reduced, though its distribution area was similar to that in monocultures, and the area of β_2 receptors was marginally smaller compared to LCn in monoculture.

Conclusions: Both temperature and the presence of astrocytes in cell culture modulate adrenergic receptor expression in the LCn, with different effects on α_{1A} and β_2 receptors. Extensive changes in intracellular LL following NA stimulation are typically attributed to AG in astrocytes, but they were also detected in the LCn.

Although lower temperature affects receptor expression in LCn, the short duration of FRET recordings makes acute effects of temperature on LL measurements unlikely. However, the absence of astrocytes in the culture during LL measurement in LCn is an important factor to consider when interpreting the results, as the presence of astrocytes also modulates receptor expression in the LCn.

Thursday, September 18th, 13:00

Molecular brain imaging in tracking neurodegenerative brain disorders

Molecular imaging of parkinsonian syndromes: differential diagnosis and beyond

Joachim Brumberg

Klinik für Nuklearmedizin, Universitätsklinikum Freiburg, Germany

The lecture explores the pivotal role of PET and SPECT imaging in the evaluation of parkinsonian syndromes. It will focus on dopamine transporter imaging, metabolic imaging and tau PET and highlight how these modalities may contribute to the differential diagnosis between idiopathic Parkinson's disease and atypical parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration. In addition to diagnostic insights, the presentation will address the emerging prognostic value of molecular imaging in predicting disease progression and therapeutic response. Advances in imaging biomarkers and their integration into clinical practice will be discussed, highlighting their importance for early and accurate diagnosis as well as personalized treatment strategies.

Healthy and disease-specific metabolic brain networks in patients with neurodegenerative disorders

Matej Perovnik

Department of Neurology, University Medical Centre Ljubljana, Slovenia

Neurodegenerative disorders encompass conditions dominated by cognitive and/or motor dysfunction. Across these diseases, FDG PET spatial covariance ("metabolic network") analyses consistently reveal reproducible, disease specific patterns that are stable across disease stages, scanners, and centers. These pathological topographies can encroach upon the default mode network (DMN), the dominant resting-state network in healthy individuals. In this lecture I will first review thirty years of research related to defining, validating, and applying metabolic brain networks at the single subject level – including recent advances in dementia with Lewy bodies. I will then consider whether relationships between disease topographies and the normative DMN can provide a novel classification framework for neurodegenerative syndromes. To illustrate, I will summarize analyses from a pooled multicenter database comprising approximately 1,200 patients with common neurodegenerative disorders and 499 age and sex matched controls. The data revealed three distinct disease categories defined by the spatial relationship of the disease-specific metabolic topography and the DMN. The relevance to diagnosis, differential diagnosis, prognosis and clinical trials will be discussed.

Exploring connectivity patterns in dual phase PET imaging

Débora Elisa Peretti

Laboratory of Neuroimaging and Innovative Molecular Tracers, University of Geneva, Switzerland

Positron emission tomography (PET) is an imaging technique that allows for the visualisation and quantification of biochemical processes of the human body, which is important for understanding the mechanisms underlying disease and normal body mechanisms. However, PET is an expensive technique that is not readily available in all centres. Therefore, there is a great need to extract as much information as possible from a single scan not only for the benefit of patients but also to reduce costs in research studies. Dual phase imaging protocols consist of acquiring one image at radiotracer injection before standard acquisition. In this way, two images are acquired: one displaying flow (early phase) and one that shows the standard image (late phase). The combination of the information provided by these images has the potential of improving diagnosis and prognosis of patients with a single scan through the identification of patterns in the images. This imaging protocol has been successfully validated and applied to amyloid-β PET scans in patients of suspected Alzheimer's disease (AD), while other radiotracers and target populations are still under study. An automated pattern identification approach is the Scaled Subprofile Modelling using Principal Component Analysis (SSM/PCA), which is a special type of network analysis that allows for the identification of disease-specific patterns. This technique has been mostly employed using metabolic PET images in Parkinson's disease and AD. However, it has been used in other radiotracers and diseases, including early phase scans. This talk will focus on the use of SSM/PCA to assess connectivity patterns in images acquired using a dual phase protocol and expanding its use to radiotracers beyond metabolic PET scans.

Extending SSM/PCA to multiclass classification of parkinsonian syndromes

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The differential diagnosis of parkinsonian syndromes—such as Parkinson's disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP)—remains a complex clinical challenge, particularly in the early stages of disease when symptoms often overlap. While 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has proven valuable in identifying disease-specific metabolic patterns, existing analytical frameworks such as the Scaled Subprofile Model/Principal Component Analysis (SSM/PCA) have traditionally been limited to binary classification tasks, thereby restricting their utility in real-world diagnostic settings. In this work, we present a novel extension of the SSM/PCA framework that enables multiclass classification, allowing for the simultaneous differentiation of multiple parkinsonian

syndromes. The method involves spatial normalization of FDG-PET images and dimensionality reduction via principal component analysis (PCA).The selected components are incorporated into a multinomial logistic regression model, which generates disease-specific metabolic topographies used to classify new patients. Rather than relying on healthy control images, our approach introduces an artificial "undetermined" reference group, constructed from averaged patient images, thereby enhancing clinical applicability.

The model was trained on a balanced cohort and validated on an independent dataset. Validation results demonstrated high diagnostic accuracy, with area under the curve (AUC) values of 0.95 for PSP, 0.93 for PD, and 0.90 for MSA. Using a 99% probability threshold for classification, the model correctly identified 82% of PD patients, 29% of MSA patients, and 77% of PSP patients, with misclassification rates of only 5–6%. Remaining cases were assigned to the undetermined group, allowing for further clinical evaluation.

These findings demonstrate that multiclass SSM/PCA is a powerful tool for both clinical decision support and research into parkinsonian syndromes. The approach can be further extended to include additional parkinsonian disorders or adapted for use in other neurodegenerative diseases, such as dementias.

Personalized network-based FDG-PET approach to differential diagnosis in neurodegenerative disorders

Tomaž Rus

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Early and accurate differentiation of cognitive and parkinsonian neurodegenerative disorders is clinically challenging. FDG-PET improves diagnostic precision but often depends on expert interpretation. Although statistical and machine learning techniques have shown promise, most existing approaches are limited to predefined disease comparisons such as PD vs. MSA vs. PSP. In this work we present a flexible framework that adapts to the specific clinical question, aiming to provide individualized diagnostic support. We analyzed an in-house FDG-PET cohort including 235 patients with Alzheimer's disease, behavioral variant frontotemporal dementia, dementia with Lewy bodies, Creutzfeldt–Jakob disease, Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, and 63 healthy controls. Each case was represented by disease-related metabolic networks such as PDRP, MSARP, PSPRP, ADRP, DLBRP, and FTDRP. Using Orange Data Mining software in Python, we applied multiple classifiers, including logistic regression, support vector machines, and Naive Bayes. For every diagnostic scenario—for example PD versus PSP or AD versus bvFTD—models were trained only on the relevant patient subsets and evaluated with leave-one-out cross-validation, yielding metrics such as AUC, sensitivity, and specificity. Several algorithms achieved high diagnostic accuracy (AUC 0.90-0.97), with specificity often remaining robust (0.80-0.92), while underperforming methods provided important feedback on the limits of current training sample sizes and highlighted directions for refinement. The resulting algorithmic framework is designed to mimic the reasoning of expert readers by integrating prior clinical probability into FDG-PET interpretation, while also delivering both global performance indicators and individualized patient-level probability outputs. This approach increases transparency of diagnostic reasoning, offers reliable support for diverse clinical scenarios, and represents a step toward more personalized and trustworthy use of machine learning in the evaluation of neurodegenerative disorders.

Thursday, September 18th, 16:45

Molecular mechanisms underlying ALS and FTD

Identification of novel RGNEF modulators through high-throughput screening of an FDA/EMA approved drug library

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Cellular modifiers of TDP-43 functionality have been found to exert a powerful action on modulating the effects of this protein in Amyotrophic Lateral Sclerosis (ALS). Recently, we have explored the connections of TDP-43 with RGNEF, a guanine nucleotide exchange factor (GEF) that is a powerful modifier of neurofilaments (NfL) mRNA stability in motor neurons and can be often found in co-inclusions with TDP-43 in ALS patients. Modulation of the endogenous levels of RGNEF were therefore investigated by pharmacological agents using a high-throughput screening (HTS) approach. A library of 1540 FDA/EMA-approved drugs (Prestwick Chemical Library) was screened on an engineered HEK-293 cell line, where endogenous RGNEF was C-terminally tagged with GFP via CRISPR-Cas9 technology. To ensure the specificity of RGNEF modulation, a parallel control cell line stably expressing mCherry was included. Assay optimization involved careful consideration of parameters such as cell number, plate coating, cellular tolerance to DMSO, and compatibility with automated workflows. Concurrently, an image analysis pipeline was developed to quantify RGNEF levels (488 nm channel) and cellular distribution, normalized by cell count (Hoechst-33342 channel), with the mCherry control quantified in the 594 nm channel. Two independent screening rounds were conducted, both demonstrating a normal distribution of the viability index and a strong inter-round correlation. Applying a 97.5% confidence level (corresponding to a Z-score viability threshold above -2.17 to exclude cytotoxic compounds), we identified 12 compounds that specifically increased RGNEF levels. Intriguingly, among these 12 identified hits, the entire class of Artemisinin-type (ART) drugs present in the library – Artesunate, Artemisinin, and Artenimol – were all found to consistently and specifically upregulate RGNEF expression, thereby demonstrating complete coverage of this drug class. These findings highlight a novel pharmacological target for ARTs and present promising leads for therapeutic intervention via RGNEF modulation. Acknowledgements This work was supported by a generous donation from the Temerty Family Foundation to MJS and EB. MJS is supported by the Canadian Institutes of Health Research (CIHR). EB is supported by the Italian ALS Association AriSLA (project NOSRESCUEALS).

FUS modulates the level of rRNA modifications and ribosome activity in health and disease

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FUS is a multifunctional protein involved in many aspects of RNA metabolism. Recently, we have shown that FUS depletion results in a change in the expression of numerous small nucleolar snoRNAs that guide post-transcriptional modifications at specific positions in rRNAs (Gawade et al., Sci Rep, 2023). Using RiboMeth-seq and HydraPsiSeq to profile site-specific 2'-O-methylation and pseudouridylation of rRNA, respectively, we demonstrated considerably higher modification at several sites in HEK293T and SH-SY5Y cells with FUS knockout (FUS KO) compared to wild-type (WT) cells. Interestingly, the rRNA modification pattern was partially correlated with the abundance of the corresponding guide snoRNAs. Furthermore, similar direction of changes in rRNA modification and snoRNA levels were observed in SH-SY5Y cells with the FUS mutation (R495X) related to the early-onset disease phenotype of amyotrophic lateral sclerosis (ALS). Next, we used the isogenic line of iPSCs derived from the patient with ALS-FUS (with the P525L mutation) further differentiated into neuronal progenitor cells (NPCs) and motor neurones (MNs). Using RiboMeth-seq and HydraPsiSeq, we analysed rRNA modification profiles and snoRNA levels in mutant NPCs and MNs compared to WT cells. Additionally, we tested the translation activity of ribosomes in mutant NPCs compared to that of WT NPCs by Ribo-seq. Our findings suggest a role for FUS in modulating rRNA modification patterns and contributing to ribosome heterogeneity that may constitute a fine-tuning mechanism for translation efficiency/fidelity. This in turn may represent a new translation-related mechanism that underlies the progression of ASL-FUS disease.

RNA mechanisms associated with *C9orf72* mutation in ALS and FTD

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) share some common genetic basis, most prominently the *C9orf72* hexanucleotide repeat expansion mutation. This mutation, consisting of GGGGCC repeats transcribed in both sense $(G_4C_2)_n$ and antisense $(C_4G_2)_n$ directions, gives rise to predominantly nuclear RNA accumulations called RNA foci, which are assumed to be pathogenic. In our recent work, we identified a novel interaction between antisense (C4G2)n RNA and phenylalanine-tRNA synthetase (FARS). This interaction impairs the charging of phenylalanine-tRNA, thereby reducing translation of proteins enriched in phenylalanine residues. Bioinformatic analyses revealed that many phenylalanine-rich proteins localize to cellular membranes, with the endoplasmic reticulum particularly affected, which we also experimentally confirm in *C9orf72* patient-derived cells. Our findings highlight the role of aminoacyl-tRNA synthetases and phenylalanine-rich proteins in *C9orf72*-linked ALS/FTD and suggest their contribution to disease mechanisms.

European Partnership for Brain Health (EP BrainHealth): advancing collaborative research, innovation and societal Impact

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Brain disorders – encompassing neurological and mental health conditions – are among the leading causes of disability and mortality worldwide. In Europe, the burden is amplified by demographic change, the aftermath of the COVID 19 pandemic, and growing socio economic pressures. The European Partnership for Brain Health (EP BrainHealth), co funded under Horizon Europe, is a ten year, transnational initiative uniting the European Commission, Member States, Associated Countries, and global partners to address these challenges through coordinated research, innovation, and policy alignment.

The partnership's vision is improved brain health for all, achieved by enhancing understanding of the brain, fostering prevention, and accelerating the translation of research into accessible, evidence based solutions for diagnosis, treatment, and care. Its mission is underpinned by a Strategic Research and Innovation Agenda (SRIA) and operationalised through nine work packages spanning funding, capacity building, stakeholder engagement, and global outreach.

A central instrument of EP BrainHealth is the Joint Transnational Call (JTC) scheme. JTCs are competitive, peer reviewed funding calls jointly launched and co financed by participating countries and the European Commission. They are designed to pool national and EU resources, promote interdisciplinarity, accelerate innovation and ensure alignment with the SRIA, targeting priority areas such as early diagnosis, personalised interventions, prevention strategies, and brain health literacy.

The Ministry of Health, as the Slovenian partner in the project, supports the creation of a structured, inclusive brain health ecosystem that bridges research, clinical practice, and societal needs. This commitment aligns with Slovenia's national priority to promote brain health across all stages of life. As a JTC funder, the Ministry will help catalyse innovative, high-impact projects, ensuring that Slovenian researchers and clinicians are integrated into a pan-European network of excellence, while advancing national goals in research, prevention, early diagnosis, and equitable access to brain health services.

Thursday, September 18th, 16:45

Advances in neuromodulation and neuroimaging in mental health

Neuromodulation and meditation: integrating insights to enhance well-being and the study of consciousnes

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The neuroscience of meditation is providing insight into the beneficial effects of meditation on well-being and informing understanding of consciousness. Despite these advances, the precise neural mechanisms linking meditation to changes in brain function remain incompletely understood. Non-invasive brain stimulation (NIBS) offers a unique approach to causally probe these mechanisms and potentially enhance meditation effects. To date, most NIBS–meditation studies have targeted frontal and parietal cortices, demonstrating that modulation of these regions can influence both neural activity and behavioral outcomes. Notably, NIBS has also revealed distinct neural signatures associated with long-term meditation experience. Future research should systematically identify the specific brain networks, oscillatory dynamics, and causal pathways underlying different forms and stages of meditation. Overall, NIBS-meditation research holds promise for enhancing meditation-based interventions in support of well-being in both non-clinical and clinical populations, and for uncovering the brain-mind mechanisms of meditation and consciousness.

Temporal dynamics of history biases in anti-NMDAR encephalitis and schizophrenia

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Human perception and memory are systematically shaped by previously experienced stimuli, a phenomenon known as history biases. One well-established example is serial dependence, in which current memory reports are subtly but consistently biased toward previously remembered stimuli [1]. Previous research has shown that, compared to healthy controls, serial dependence in spatial working memory is reduced in patients with anti-NMDAR encephalitis and reversed in patients with schizophrenia. These findings suggests that NMDA receptor hypofunction may be a shared pathological mechanism underlying altered serial dependence in these disorders [2]. Importantly, history biases are not limited to the immediately preceding trial; they can also reflect the accumulated influence of multiple past trials on behavior [3]. These different temporal scales likely reflect distinct memory mechanisms and may offer complementary insights into cognitive dysfunction in anti-NMDAR encephalitis and schizophrenia. In this study, we model behavioral performance in a spatial working memory task in patients and healthy controls using two history biases: a short-term bias, spanning a few seconds, and a long-term bias, extending across minutes. We expect the short-term bias to replicate previously reported group differences in serial dependence [2], and we explore whether the long-term bias exhibits a similar pattern. Preliminary results indicate that both short- and long-term history biases significantly influence behavior on the current trial across all participant groups. However, only the short-term bias reliably distinguishes between patient groups, reinforcing its potential as a sensitive marker of NMDA-related cognitive dysfunction.

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Spontaneous and perturbation-based electroencephalographic markers of brain health

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Understanding the neurophysiological basis of brain health is essential for developing sensitive, non-invasive biomarkers of vulnerability and resilience. This work leverages electroencephalography (EEG) combined with transcranial magnetic stimulation (TMS) to probe brain function beyond passive observation, using controlled perturbations to evoke dynamic cortical responses. In healthy individuals, heightened prefrontal reactivity to TMS prior to the COVID-19 pandemic predicted worse mental health trajectories during the crisis, supporting a novel, biologically grounded model of brain resilience. In schizophrenia, task-driven EEG responses uncovered specific inhibitory dysfunctions during working memory, enabling accurate individual-level classification through interpretable machine learning. Notably, the temporal EEG features driving this classification aligned with known alterations in alpha-band modulation. Across studies, perturbation-evoked markers demonstrated superior sensitivity in capturing clinically relevant variability compared to spontaneous EEG alone. This work positions the combination of neuroimaging and non-invasive brain stimulation as powerful tool for brain health research, enabling early detection of vulnerability, characterization of neuropsychiatric dysfunction, and identification of potentially modifiable targets within a precision-based approach to mental health.

Emulation of emotions in patients with depression and healthy controls

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Emotion dysregulation is a transdiagnostic symptom of psychiatric disorders that cuts across diagnostic categories. It is associated with increased suicidality and poor treatment outcomes across treatment modalities. In fact, some researchers have posited that all psychiatric disorders include elements of emotion dysregulation. Despite an increased research into this phenomenon in recent decades, our understanding of neurocognitive processing of this disorders remains underexplored. One possible reason for this is the lack of ecological validity of existing paradigms for elicitation and measurement of emotion dysregulation. We conducted two studies reflecting on the ecological validity of standardized emotion processing and regulation paradigms. First, qualitative phenomenological data revealed that the central process that both normative participants and patients with affective disorders engage in is voluntary construction of emotional response (i.e., emulation). This qualitative observation was borne out by quantitative measurements. We find that subjectively reported arousal during standardized emotion processing tasks is associated with a) subjective construction of emotional response mediated by conceptual understanding of the stimuli; and b) participants' susceptibility to demand characteristics (i.e., modifying their behavior in accordance with perceived research questions and hypotheses of the study). These observations were extended to underlying electrophysiological measurements. People who are susceptible to demand characteristics exhibited an increase in event-related potentials associated with intermediate emotion processing. Furthermore, voluntary construction of emotional response (despite being associated with an increase in subjectively reported arousal) exhibited reduced event-related potentials associated with emotion processing.

Changes in microRNA expression after TMS treatment of depression

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Research on the molecular mechanisms underlying transcranial magnetic stimulation (TMS) therapy for depression has revealed significant changes in microRNA (miRNA) expression profiles. These represent a crucial epigenetic mechanism influencing neuroplasticity through which TMS exerts its therapeutic effect. Multiple preclinical studies have demonstrated that repetitive TMS (rTMS) induces specific changes in miRNA expression in different cortical regions, with repeated sessions producing even more substantial changes in expression of several specific miRNAs in comparisson to single TMS session. Moreover clinical studies in treatment resistant depression with rTMS have identified several miRNAs as potential biomarkers for it's treatment response like miR-16-5p, miR-17-5p, miR-221-3p and miR-124 among others suggesting that miRNA profiling could serve both as predictive biomarkers for treatment selection and mechanistic indicators of therapeutic response in TMS therapy for depression, potentially enabling personalized treatment approaches based on individual epigenetic profiles.

Friday, September 19th, 10:00

ALS beyond motor neurons: respiratory, cognitive, and clinical perspectives

Epidemiology of ALS, what's new?

Andrea Calvo

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ALS/MND is still a rare disorder, but epidemiologists reported a constant increase in incidence, particularly in emergent countries. ALS predominantly affects older adults, so its prevalence is expected to increase as the population ages. However, improvements in survival rates must also be considered, as they may significantly alter previous projections of ALS prevalence. Some recent data reveal that by 2040, ALS prevalence will rise by a median of 25% compared to previous estimates. These rates may change if new treatments are discovered or if a region modifies its capacity to provide care, such as by expanding access to multidisciplinary treatment. While ALS will remain a rare disease, it will likely become significantly more common than it is today. These projections should inform future health policy planning and the organization of ALS care centres. Moreover, some studies reported some geographic distribution of ALS, suggesting that the role of environment is truly a factor. The epidemiological studies on ALS focused also the attention on the genetic distribution of familial cases all over the world.

This overview will cover the most relevant epidemiological aspects on ALS/MND spectrum.

Phenotypic and cognitive determinants of social cognition in amyotrophic lateral sclerosis: a population-based study

Francesca Palumbo, Barbara Iazzolino, Anastasia Dei Giudici, Stefano Callegaro, Antonio Canosa, Umberto Manera, Rosario Vasta, Enrico Matteoni, Sara Cabras, Giorgio Pellegrino, Emilio Minerva, Alessandra Maccabeo, Giuseppe Fuda, Federico Casale, Cristina Moglia, Adriano Chiò, Andrea Calvo

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Background: Deficits in social cognition (SC) are included in the revised diagnostic criteria for the amyotrophic lateral sclerosis–frontotemporal spectrum disorder (ALS-FTSD). However, the cognitive and behavioural correlates of SC, as well as its contribution to cognitive classification, remain unclear. This cross-sectional study investigated the impact of SC assessment on ALS-FTSD categorization and examined its relationship with executive functions (EF) and behavioural changes.

Methods: A total of 259 ALS patients and 103 healthy controls from the Turin ALS Centre underwent cognitive and behavioural assessments, including SC domains: facial emotion recognition (FER) and cognitive/affective theory of mind (ToM). Deficits were defined as performance ≥2 SD below the normative/control mean.

Results: ALS patients performed significantly worse than controls in all SC domains ($p < 0.001$), particularly in recognizing fear, anger, disgust, and sadness ($p < 0.008$). ToM and FER deficits were observed in 22% and 31% of patients, respectively; 11% had both. Male sex was associated with poorer FER performance ($p < 0.006$), while older age and lower education correlated with ToM impairments ($p < 0.001$). SC deficits were behaviourally associated with perseverative and dysexecutive traits ($p < 0.001$), but showed no clear cognitive predictors. SC assessment reclassified 9.8% of cognitively normal and 19.5% of behaviourally impaired patients.

Conclusions: SC assessment identifies clinically meaningful deficits in ALS patients and can significantly impact cognitive classification, with consequences on prognosis and end-of-life management.

Predicting cognitive function in ALS: the role of respiratory and laboratory measures

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Amyotrophic lateral sclerosis (ALS) is a multisystem neurodegenerative disease primarily affecting the motor system. Up to half of patients show cognitive impairment, most often in executive functions, verbal fluency, and language (ALS-specific domains), while memory and visuospatial abilities (ALS-nonspecific domains) are usually preserved. The determinants of cognitive dysfunction are not fully understood. Disease progression, functional status, and bulbar onset have been implicated, but the predictive roles of respiratory function and cerebrospinal fluid neurofilament light chain (NfL) levels remain unclear. NfL is a biomarker of neurodegeneration and survival in ALS and may also reflect risk of cognitive decline. Respiratory insufficiency has likewise been linked to cognition, though results are inconsistent.

This study investigated the association of respiratory function and NfL with cognition in ALS. Clinical, demographic, and cognitive data (Edinburgh Cognitive and Behavioural ALS Screen, ECAS) were retrieved from 141 patients treated at the Institute of Clinical Neurophysiology, University Medical Centre Ljubljana. Forced vital capacity (FVC) measured by spirometry was available for all patients, and NfL levels for 59. FVC significantly predicted global cognitive performance ($B = 0.23$, $SE = 0.07$, $p < .001$), independent of age and functional status. Each 1% increase in FVC corresponded to a 0.23-point higher ECAS score. FVC also predicted performance on ALS-specific domains ($B = 0.19$, $SE = 0.05$, $p < .001$) and showed a weaker trend for ALS non-specific domains ($B = 0.03$, $SE = 0.02$, $p = .087$). Patients without respiratory insufficiency performed better globally, with significant advantages in executive and language subdomains. NfL levels were not significant predictors of global cognition, though trends were observed for ALS-specific domains.

In summary, reduced respiratory function, particularly measured by FVC, is associated with poorer cognition in ALS, especially in executive and language domains. This corresponds to findings in healthy individuals, where elevated CO_2 levels have a detrimental effect on executive functions. The predictive value of NfL for cognitive impairment remains inconclusive and requires further investigation.

Influence of upper and lower motor neuron damage pattern on respiratory impairment and survival in patients with ALS

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Background: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that affects upper motor neurons (UMNs) and lower motor neurons (LMNs). The disease phenotype varies among patients, with some showing predominantly UMN involvement, others LMN involvement, and some a combination of both. Respiratory failure is the leading cause of mortality in ALS, often due to diaphragmatic weakness, nocturnal hypoventilation and sleep-disordered breathing. While the overall influence of ALS phenotype on disease progression and survival is well established, the specific impact of distinct UMN and LMN involvement patterns on respiratory impairment and outcomes remains insufficiently understood.

Objectives: This study aimed to identify key prognostic factors associated with respiratory failure in ALS, focusing on the relationship between UMN and LMN involvement patters and survival. Specifically, we evaluated the prognostic value of motor neuron involvement and survival.

Methods: Approximately 300 patients with ALS, treated at the Institute of Clinical Neurophysiology, University Medical Centre Ljubljana, between January 2010 and March 2025, were observed retrospectively. The exclusion criteria were comorbiditeswith a significant influence on ALS survival or development of respiratory insufficiency, use of invasive mechanical ventilation or treatment with tofersen. The patients were classified into three groups: predominantly lower motor neuron damage (LMN), predominantly upper motor neuron damage (UMN), or mixed involvement. The motor neuron damage pattern was evaluated at two time points: at the onset and at the time of respiratory impairment (initiation of non-invasive mechanical ventilation – NIV). Bulbar and cervical regions were studied, while lumbar region was omitted from the evaluation as it has less impact on breathing than the other two. Survival analysis was performed from disease onset to NIV initiation and from NIV initiation to death or the end of observation.

Results: The Kaplan-Meier method shows that there are statistically significant differences in time to NIV initiation based on the motor neuron damage pattern at the onset of the disease ($p = .012$). Time from disease onset to initiation of NIV is the longest in patients with predominant LMN damage pattern, followed by the UMN group, and shortest in those with the mixed pattern. Time form NIV initiation to death is the shortest in patients with predominantly LMN involvement, followed by those with mixed pattern, and the longest in patients with predominantly UMN involvement. However, the Kaplan-Meier method does not reveal statistically significant differences ($p = .17$).

Conclusion: While the precise biological underpinnings require further investigation, our results may imply that the loss of central plasticity, often associated with UMN degeneration, has less compensatory reserve for maintaining breathing capacity than peripheral mechanisms related to LMN integrity. This could explain the earlier need for ventilatory support in patients with significant UMN involvement.

Diaphragm ultrasound: functional assessment in ALS patients

Gregor Omejec

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Respiratory failure is the leading cause of morbidity and mortality in amyotrophic lateral sclerosis (ALS). Early detection of respiratory muscle dysfunction is therefore essential for timely initiation of ventilatory support and for optimizing patient management. While conventional pulmonary function tests, such as forced vital capacity and sniff nasal inspiratory pressure, remain standard tools, they may underestimate early diaphragmatic impairment and are often difficult to perform in advanced disease stages. Diaphragm ultrasound has emerged as a reliable, non-invasive, and repeatable method to assess respiratory muscle structure and function in ALS.

Key parameters include diaphragm thickness at rest and during inspiration, thickening fraction as an index of contractility, and diaphragm excursion during quiet and deep breathing. These measurements correlate with traditional respiratory function tests and can predict the need for non-invasive ventilation. Importantly, ultrasound can be performed at the bedside, even in patients unable to cooperate with volitional maneuvers, offering clear advantages in advanced disease.

Emerging data suggest that serial diaphragm ultrasound provides valuable information on disease progression and may serve as a biomarker for clinical trials. Limitations include operator dependency and the need for standardized protocols.

Diaphragm ultrasound represents a promising tool for functional respiratory assessment in patients with ALS. Its integration into routine clinical practice may enhance early detection of respiratory decline, improve patient monitoring, and guide therapeutic decision-making.

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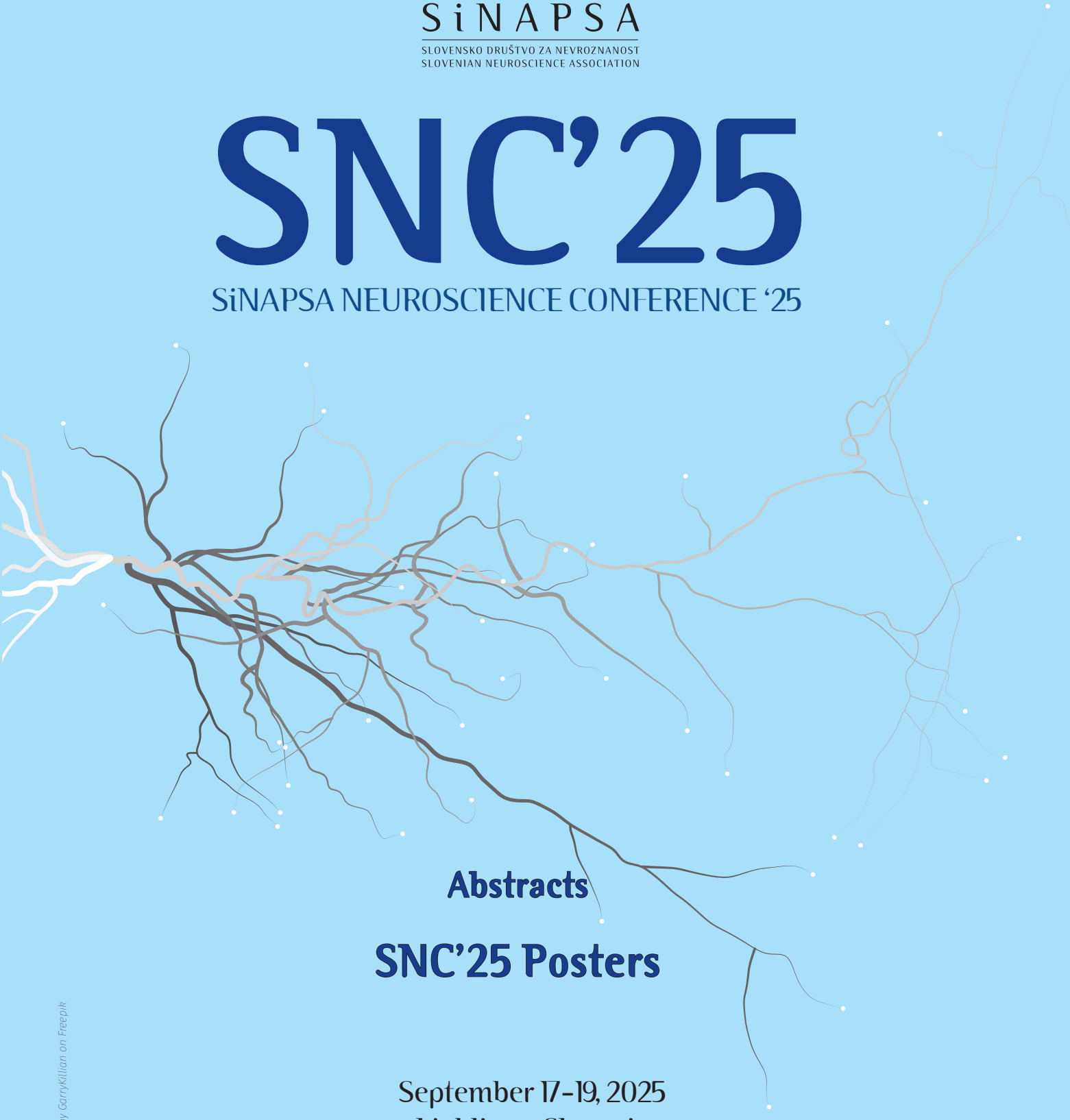

Abstracts

SNC'25 Posters

September 17-19, 2025
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CEL.01 Thursday, September 18th, 15:00 [Cellular Neuroscience A]

Interplay of γ-enolase and cathepsin X in M1/M2 polarized microglia

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Neuroinflammation is a complex immune response within the central nervous system, primarily mediated by microglia. In response to various stimuli, microglia polarize into either pro-inflammatory M1 or anti-inflammatory M2 phenotypes. M1 microglia secrete cathepsin X, a lysosomal peptidase that cleaves the C-terminus of γ-enolase, a glycolytic enzyme with neurotrophic-like properties, thereby abolishing its neurotrophic activity. However, the roles and regulation of these proteins in activated microglia remain unclear. In this study, we investigated the expression, secretion, and subcellular localization of γ-enolase and cathepsin X in BV2 microglial cells. M1 polarization was induced by lipopolysaccharide or interferon-γ, while M2 polarization was triggered by interleukin-4 or interleukin-13. Cathepsin X activity decreased in a time- and concentration-dependent manner following pro-inflammatory stimulation, whereas higher concentrations of M2 stimuli caused a slight increase. Similarly, γ-enolase expression and secretion were modulated by both pro- and anti-inflammatory signals, where its release was also time- and concentration-dependent. Pharmacological inhibition of cathepsin X with AMS36 attenuated neurotoxic microglial polarization, marked by reduced expression of M1 markers, and enhanced expression of M2 markers. It also altered the expression and secretion patterns of active γ-enolase in both phenotypes. Using an indirect co-culture model, we demonstrated that conditioned media from M2-polarized microglia promoted neurite outgrowth and reduced cytotoxicity in differentiated Neuro-2a cells, whereas media from M1-polarized exerted inhibitory and neurotoxic effects, identifying γ-enolase as a polarization-dependent microglial factor contributing to neurotrophic support. These findings highlight the interplay of γ-enolase and cathepsin X in microglial activation, suggesting their potential as therapeutic targets in neuroinflammation-associated neurodegeneration.

Keywords: neuroinflammation, microglia, γ-enolase, cathepsin X

CEL.03 Thursday, September 18th, 15:00 [Cellular Neuroscience A]

The role of tenascin-C in the structural plasticity of perineuronal nets in the hippocampus

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Neuronal plasticity is a fundamental property of the nervous system that enables it to change in response to stimuli by reorganizing its structures, functions, and connections. Among the key regulators of neuronal plasticity are perineuronal nets (PNNs), condensed forms of the extracellular matrix (ECM), also containing the ECM glycoprotein tenascin-C (TnC), which has been shown to modulate synaptic plasticity in the hippocampus. The aim of this study was to investigate the role of TnC in hippocampal PNN expression in TnC-deficient (TnC -/-) and wild-type (TnC +/+) mice after housing from postnatal day 21 in enriched or standard environments (EE and SE, respectively) for four weeks. Results showed that PNNs expressed in the dentate gyrus (DG), CA1, and CA2 regions of the hippocampus in TnC-/- mice housed in SE exhibited increased intensity compared to TnC+/+ mice in the same condition. Additionally, this increase in PNN intensity was reduced in the TnC-/- group housed in EE, suggesting a compensatory effect of environmental stimulation on PNN expression in the absence of TnC. No significant changes were observed in the CA3 region. Taken together, these findings highlight the important regulatory role of TnC in PNN expression in the hippocampus of young adult mice. TnC appears to help maintain the condensation state of PNNs during development, with environmental enrichment (EE) serving as a potential compensatory mechanism in cases of TnC deficiency.

CEL.05 Thursday, September 18th, 15:00 [Cellular Neuroscience A]

High extracellular K^+ triggers metabolic and morphological changes in brain cells

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Neuronal information processing is driven by action potentials, a highly energy-demanding process accompanied by a rise in the local extracellular potassium concentration ($[K^+]_{out}$) due to K^+ efflux from neurons. The impact of this $[K^+]_{out}$ increase on brain cell function remains incompletely understood. We examined how elevated $[K^+]_{out}$ affects brain cell signalling, metabolism and morphology in isolated rat cortical astrocytes and in astrocytes and neurons in *Drosophila* brains, using fluorescent sensors for Ca^{2+}, cyclic adenosine monophosphate (cAMP), D-glucose, and L-lactate in combination with real-time confocal microscopy.

Exposure to elevated $[K^+]_{out}$ (15 and 50 mM) triggered increases in intracellular Ca^{2+} and cAMP in rat cortical astrocytes. Similarly, in *Drosophila* brains, 15 mM $[K^+]_{out}$evoked Ca^{2+} and cAMP elevations in both astrocytes and neurons. The Ca^{2+} rise was comparable in amplitude across both cell types but occurred ~10-fold faster in neurons. Neuronal cAMP increases exhibited ~3-fold greater amplitudes and ~20-fold faster kinetics than those in astrocytes. In rat astrocytes, elevated $[K^+]_{out}$ also increased intracellular levels of free D-glucose and L-lactate, indicating facilitated glucose uptake and enhanced aerobic glycolysis. In *Drosophila* brains, 15 mM $[K^+]_{out}$ led to a rise in intracellular L-lactate in both astrocytes and neurons, with similar kinetics, suggesting activation of aerobic glycolysis in both cell types. However, while astrocyte glucose levels remained unchanged, neuronal glucose levels decreased, consistent with K^+-induced glucose consumption. Morphologically, elevated $[K^+]_{out}$ induced a ~15% increase in astrocyte cell volume and ~40% elongation of astrocyte processes.

These findings show that elevated $[K^+]_{out}$ activates Ca^{2+} and cAMP signalling and promotes aerobic glycolysis in brain cells, supporting lactate availability during heightened neuronal activity. The $[K^+]_{out}$-induced morphological changes in astrocytes may alter extracellular nanoarchitecture and enhance metabolite diffusion, facilitating metabolic support under increased energy demand.

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CEL.07 Thursday, September 18th, 15:00 [Cellular Neuroscience A]

L-lactate and GPR27 agonists modulate citrate production in 3T3 cells and astrocytes

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Astrocytes are neuroglial cells with many homeostatic functions, including the regulation of brain energy metabolism. Astrocytes can convert D-glucose to L-lactate in a process known as aerobic glycolysis[1]. In culture, and likely *in vivo*, astrocytes represent the main source of mitochondrial citrate production and its secretion into the intercellular space. Citrate, which is produced in the Krebs cycle, is involved in the regulation of glycolysis and gluconeogenesis. Although the concentration of citrate in the cerebrospinal fluid is relatively high, ranging from several tens to several hundred µmol/L, its precise role remains unclear[2,3]. It has been shown that aerobic glycolysis in astrocytes can potentially be activated with certain G-protein coupled receptor (GPCR) agonists, including those activated by noradrenaline and L-lactate[4,5]. GPR27 is an orphan GPCR and a member of the super-conserved receptors expressed in the brain (SREB). It has been shown that stimulation of GPR27 enhances aerobic glycolysis and L-lactate production in 3T3 murine embryonic fibroblasts (MEF) and astrocytes[5]. Here, we investigate the impact of the stimulation with extracellular L-lactate and GPCR surrogate agonists on the production of citrate in astrocytes and 3T3 cells. We used a genetically encoded fluorescent biosensor to monitor cytosolic citrate with high temporal resolution in single cells. Cells were stimulated with L-lactate (2 mM) and GPR27 surrogate agonists (1 µM). Our preliminary results show that extracellular L-lactate significantly increases [citrate]i in 3T3 cells and rat astrocytes. Similarly, stimulation of GPR27 with surrogate agonists also increases [citrate]i in 3T3 cells and rat astrocytes. These results indicate that L-lactate and GPR27 receptor activation modulate mitochondrial citrate production, which may affect energy metabolism in the cell itself and, under *in vivo* conditions, more broadly in the brain.

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CLI.01 Thursday, September 18th, 15:00 [Clinical Neuroscience A]

Coexisting subdural hematoma in cerebral amyloid angiopathy: a case series

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Background: Cerebral amyloid angiopathy is a rare neuro-vascular diorder characterised by beta amiloid deposition within the wall of leptomeningeal and small cortical vessels, making patients more prone to bleeding due to fragile vascular wall. Diagnosis of CAA is estabilised by Boston criteria which rely on clinical presentation, imaging and patohistological findings, however they do not do not include subdural hematoma (SDH) as a diagnostic feature.

Objective: To report three consecutive cases of CAA presenting with concurrent lobar ICH and acute SDH.

Methods: Retrospective case series at a single tertiary center over two months. Three patients (63–77 years) with acute lobar ICH and SDH underwent surgical evacuation. Histological confirmation of CAA was obtained in all cases.

Results: All three presented with sudden focal deficits and imaging showing lobar ICH plus SDH. Neurosurgical evacuation was performed without intraoperative complications. Histopathology demonstrated amyloid-β deposition in leptomeningeal and cortical vessels, confirming CAA. At discharge, two patients had moderate disability (mRS 3) and one made a good recovery (mRS 2).

Conclusions: The clustering highlights a potentially under-recognized association between CAA and acute SDH. Including SDH in future diagnostic criteria may facilitate earlier diagnosis and tailored management.

Keywords: cerebral amyloid angiopathy, subdural hematoma, lobar intracranial hemorrhage

CLI.03 Thursday, September 18th, 15:00 [Clinical Neuroscience A]

The miRNA 216b-5p acts as a tumor-suppressor by manipulating cell cycle progression in glioblastoma cells

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Background: Glioblastoma is the most common brain tumor in adults and with an approximate survival rate of 15 months, new treatment strategies are of utmost urgency. In our previous phase II clinical trial, applying immunotherapy with dendritic cells to glioblastoma patients, no differences in overall survival were observed. However, distinct miRNAs and in particular miR-216b, harbored predictive power and were associated with therapy susceptibility. Thus, we hypothesize that amongst others, miR-216b is involved in glioblastoma aggressiveness and thereby impacting therapeutic success.

Methods: First, we screened glioblastoma tissue samples (n=128) and several cell models for the expression of 5 different miRNAs. As miR-216b was generally low expressed compared to others, we investigated whether transfection with miR-216b "mimic" (upregulation) or "inhibitor" (blocking) had an impact on clonogenic survival, sphere-forming and migratory capacity in three patient-derived and 2 immortalized glioblastoma cell models. To gain deeper knowledge about miR-216b targets, miRNA sequencing was performed. Subsequently, predicted targets were confirmed by Western Blot, FACS analysis and drug sensitivity assays.

Results: MiR-216b upregulation resulted in reduced cell proliferation and migration as well as in decreased stemness characteristics in the investigated glioblastoma models. miRNA sequencing predicted target genes that are involved in cell division (e.g. CDK4). Accordingly, protein levels of CDK4 and subsequently phosphorylation of Rb were reduced, accompanied by an increase of cells in G0/G1 phase upon transfection with "miR-216b mimics". When miR-216b was blocked, the sensitivity towards CDK4/6 inhibitors was distinctly increased, pointing towards a drug-targeting engagement.

Conclusion: Our data indicate miR-216b acting as tumor suppressor via inhibition of CDK4 in glioblastoma cells. The prognostic and predictive value of this miRNA in glioblastoma is currently under investigation

Keywords: miRNA, primary cell culture, brain cancer

CLI.05 Thursday, September 18th, 15:00 [Clinical Neuroscience A]

Does personalized TMS offer superior therapeutic outcomes compared to conventional TMS protocols in depression?

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Background: Major depressive disorder (MDD) is a highly prevalent condition that impairs emotional, cognitive, and social functioning. While standard treatments, pharmacotherapy and psychotherapy, are effective for many, a substantial proportion of patients experience treatment-resistant depression (TRD). In such cases, non-invasive brain stimulation (NIBS) techniques, such as rTMS, approved by the FDA in 2008, and TBS, approved in 2018, offer alternative therapeutic options.

Objective: This study compares the efficacy and efficiency of novel rTMS and TBS protocols, including accelerated and add-on approaches, with standard protocols, with a focus on personalized interventions aimed at reducing time and cost burdens.

Methods: A systematic review was conducted following PRISMA guidelines. Nine studies published since 2018 were selected from PubMed and other sources. Eligible studies included TRD patients receiving accelerated or add-on rTMS/TBS. Outcomes assessed were depression severity (MADRS, HAM-D/HDRS, QIDS-C), response, and remission rates.

Results: Accelerated and combinatory protocols were found to significantly reduce depressive symptoms and improve remission rates, while maintaining safety and tolerability. Although direct comparisons with standard protocols did not yield statistically significant differences, the evidence supports a trend toward more flexible, individualized treatments, such as neuronavigated accelerated rTMS, which improve precision and reduce treatment duration.

Conclusion: Personalized and accelerated rTMS protocols show promise as efficient alternatives to conventional approaches in TRD. Further research is needed to refine

stimulation parameters and identify predictive biomarkers, supporting the advancement of precision neuromodulation in MDD treatment.

Keywords: major depressive disorder, depression, non-invasive brain stimulation, transcranial magnetic stimulation, transcranial direct current stimulation, theta burst stimulation

COG.01 Thursday, September 18th, 15:00 [Cognitive Neuroscience A]

CT-optimal touch modulations on somatosensory-motor integration and proprioception and the role of vision

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CT-optimal touch, gentle stroking at 1–10 cm/s that activates C-tactile fibers, may shape body representation and enhance multisensory integration. The effects of CT-optimal touch on sensorimotor integration and proprioception, and the influence of vision on these processes, have yet to be systematically explored. To investigate this, sighted and blind participants performed an elbow joint position-matching task by replicating two reference angles (105°,75°), measured with a universal goniometer. The experiment included three conditions: baseline (each angle reproduced three times), CT-optimal touch (gentle brushing at 3 cm/s over 18 cm of the arm for 90 seconds between trials), and non-CT-optimal touch (brushing at 18 cm/s over the same area and duration). We measured bias as mean difference between real angle and perceived one, while precision as standard deviation of their measurements. In sighted individuals, we found a significant main effect of condition, which showed that the bias was reduced in the CT-optimal condition compared to baseline. There was a trend toward a main effect of condition on precision; greater precision was associated with higher pleasantness ratings in the CT-optimal condition. In the blind group, a significant interaction emerged between group and blindness onset (late vs. early) for precision. Late blind individuals demonstrated greater precision than early blind individuals in both baseline and CT-optimal touch conditions. We conclude that, in sighted individuals, interoceptive affect contributes to stabilizing perception. However, vision appears to play a crucial role in shaping the modulatory effects of CT-optimal touch, as well as in sensorimotor integration and proprioception.

Keywords: touch, sensorimotor, proprioception

COG.03 Thursday, September 18th, 15:00 [Cognitive Neuroscience A]

High evening smartphone use drives sleep debt and lower morning affect in athletes

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In athletic populations, adequate sleep is critical for optimizing performance, recovery, and emotional well-being. However, behavioural habits such as late-night smartphone use may disrupt sleep architecture and circadian alignment, leading to the accumulation of sleep debt and impaired morning functioning. This study examined the relationship between pre-sleep smartphone use, sleep debt, and morning affect in athletes. A sample of 174 Portuguese athletes (aged 15–65) competing at national or higher levels completed validated questionnaires assessing sleep behaviour, circadian preference, and smartphone use. Sleep debt was calculated as the difference between work/school day and free-day sleep duration. Morning affect was measured using a single-item morning state rating. Participants were classified as high (daily use before bed) or low/moderate (1-6 times/week) smartphone users. Spearman correlations, linear regression, and structural equation modelling (SEM) tested associations and interactions, controlling for age, sex, chronotype, and training factors. High smartphone users showed significantly greater sleep debt ($p = .008$) and lower morning affect ($p = .004$) compared to low/moderate users. Sleep debt was negatively associated with morning affect ($\rho = –0.21$). The association was strongest in the high-use group ($\rho = –0.30$), while negligible in the low/moderate group. However, SEM revealed no significant indirect effect of smartphone use on morning affect via sleep debt. Frequent pre-sleep smartphone use in athletes is linked to greater sleep debt and lower morning affect, yet sleep loss alone may not explain this. Addressing evening screen habits can improve emotional recovery, sleep quality, and performance readiness in athletes.

Keywords: smartphone use, sleep debt, mornign affect, athletes, circadian disruption

COM.01 Thursday, September 18th, 15:00 [Computational Neuroscience A]

Exploring electroencephalographic (EEG) models of brain activity using automated modelling techniques

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Electroencephalography (EEG) is a clinical, non-invasive, high-temporal resolution technique for measuring whole-brain activity. However, the underlying mechanisms that give rise to the observed high-level rhythmic activity remain incompletely understood. Various neural population and network models attempt to explain these dynamics, but, to our knowledge, they have not been systematically explored or evaluated. To explore the space of proposed and potential models, we represent brain networks as graphs, where nodes correspond to brain sources obtained via EEG source analysis, in our case the dipole fitting of independent components. Each node's dynamics are further categorized into three subdynamics: synapto-dendritic dynamics (input transformation), intrinsic dynamic, and firing response (output transformation). These subdynamics are defined by a bounded set of functions derived from the literature, or generated by an unbounded probabilistic context-free grammar. Such a modular and unbounded specification allows for flexible construction of the network, which is consistent with the physiological laws of the human brain dynamics. Next, we repeatedly sample potential EEG models using MCMC and optimize the model parameters using CMA-ES algorithm. The objective function is dependent on the task and the EEG features of interest. We are currently utilizing our Julia-based framework and are in the model evaluation phase. The dataset consists of 64-channel EEG recordings from 50 participants performing a visual flickering task, designed to induce steady-state visual evoked potentials (SSVEP). By the time of the conference, we aim to determine which established and previously unexamined whole-brain activity models can reproduce robust and interesting features observed in this dataset.

Keywords: electroencephalography (EEG), automated modelling, neural mass models

MOL.01 Thursday, September 18th, 15:00 [Molecular Neuroscience A]

Evaluation of nociception in a model of Parkinson's disease for the study of non-motor symptoms in TRPV4-/- animals

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Parkinson's disease (PD) is a neurodegenerative disorder of the central nervous system. The PD patients also suffer from non-motor symptoms, such as pain. Traditional PD models often present motor deficits, which can compromise the assessment of nociception. A role for the TRP4 receptor has been studied in the PD model. This study aimed to investigate the role of the TRPV4 receptor in regulating nociception experimental PD model for the study of non-motor symptoms. We used female and male mice C57BL/6 KO for TRPV4 and mice C57BL/6 wild type induced by 6-OHDA bilateral injection into the striatum. Behavioral analysis was performed at baseline and on the 7th, 14th, and 21st days after induction. The rotating cylinder test evaluated possible motor function and balance deficits. The mechanical allodynia was assessed using the Von Frey filament's up-and-down method. Heat allodynia was assessed using the heating plate test at a constant temperature of 38º degrees (CEUA protocol 3164260423).Euthanasia and collection of samples for PCR and immunohistochemistry occurred on the 21st day after induction. Our results did not demonstrate significant differences in forced locomotion between groups on the days evaluated after PD induction, indicating the absence of substantial locomotor damage. The peak of mechanical allodynia was different for males and females DP WT mice, 21 and 7 days after induction, respectively.

Keywords: Parkinson, neurodegeneration, pain

MOL.03 Thursday, September 18th, 15:00 [Molecular Neuroscience A]

Novel proteins involved in the FUS-mediated biogenesis of sdRNAs in human cells

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SnoRNA-derived small RNAs (sdRNA) are 25-35 nt noncoding RNAs, processed from snoRNAs (small nucleolar RNAs). They may function as microRNAs and regulate gene expression, however, their biogenesis remains unclear. Recently, in FUS-depleted cells (FUSKO) we have observed differential expression of numerous snoRNAs followed by an altered level of corresponding sdRNAs, suggesting FUS involvement. FUS is a multifunctional protein involved in many pathways of RNA metabolism, localized mainly in the cell nucleus. Interestingly, there are mutations in the FUS gene that trap FUS in cytoplasmic aggregates; some of them have been associated with the neurodegenerative disease amyotrophic lateral sclerosis (ALS). In ALS-FUS cellular models, we also detected changes in snoRNA and sdRNA levels. To investigate the mechanism of FUS-mediated sdRNA biogenesis, we performed RNA antisense purification (RAP) of selected snoRNAs from SH-SY5Y WT and FUSKO cells followed by mass spectrometry to identify snoRNA-¬interacting proteins. This approach revealed four candidates potentially involved in sdRNA biogenesis: RALY, ILF3, DDX27 and DHX30. We validated their interaction with FUS via immunoprecipitation and assessed how FUS affects their expression at both mRNA and protein levels. Moreover, we analyzed how ALS-linked FUS mutations (FUS^{P525L} and FUS^{R495X}) alter these interactions using CRISPR-engineered cells. Given the cytoplasmic localization of FUS in ALS, we tested the subcellular localization of selected proteins by immunofluorescence. The results obtained enable us to indicate novel FUS-interacting proteins which participate in the processing of snoRNAs into sdRNAs. It will bring us closer to the mechanism of sdRNA FUS-mediated biogenesis and its role in the pathology of ALS.

MOL.05 Thursday, September 18th, 15:00 [Molecular Neuroscience A]

Role of the FUS in rRNA modifications and ribosome activity in ALS model

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Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder that affects motor neurons in the brain, brainstem, and spinal cord. Currently, there is no cure for this progressive and fatal disease. ALS is genetically heterogeneous, with mutations in multiple genes contributing to its pathology. In this study, we focus on understanding the molecular mechanisms underlying ALS, particularly those associated with mutations in the Fused in Sarcoma (FUS) gene. As a model, we are using patient-derived induced pluripotent stem cells (iPSCs), harbouring FUS mutations, which were differentiated into neuronal progenitor cells (NPCs) and subsequently into motor neurons. Previous studies have shown that FUS regulates the expression of a subset of small nucleolar RNAs (snoRNAs), which influence specific ribosomal RNA (rRNA) modifications. These alterations can impact ribosome composition and function ultimately resulting in changes in protein folding and translation efficiency. To explore these effects, we tested translation activity in FUS-mutant NPCs compared to their isogenic wild-type (WT). Our results indicate that FUS influences rRNA modification patterns, contributing to ribosome heterogeneity. This may represent a mechanism for fine-tuning translational fidelity and efficiency. Understanding how FUS dysfunction can alter ribosome.

MOL.07 Thursday, September 18th, 15:00 [Molecular Neuroscience A]

TDP-43 posttranslational modifications in stress

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Neurodegenerative diseases such as ALS are characterised by the accumulation of misfolded RNA-binding proteins that lead to neuronal dysfunction and cell death. Many of these proteins undergo post-translational modifications (PTMs) such as phosphorylation, ubiquitination or acetylation. This can significantly alter their functional properties and interaction networks. In addition, PTMs are essential mediators of protein phase separation and protein aggregation. TDP-43 is hyperphosphorylated at its C-terminus in disease. Through bioinformatic search and analysis, we found that TDP-43 is also susceptible to other PTMs that could strongly influence its function and aggregation. To this end, we exposed HEK293 and SH-SY5Y cells to various stressors that mimic acute and chronic stress. Using techniques such as two-dimensional electrophoresis coupled with Western blots, we observed different patterns of TDP-43 corresponding to different PTM profiles. Interestingly, additional bands appeared upon stress, some of which correspond to hyperphosphorylation of TDP-43, while certain bands correspond to a new modification that alters the molecular weight rather than the charge of TDP-43. Our results suggest the presence of interesting PTMs that could significantly influence disease development and possibly TDP-43 aggregation. Our study emphasises the important role of PTMs of RNA-binding proteins in ALS and FTD.

Keywords: TDP-43, PTM, ALS

MOL.09 Thursday, September 18th, 15:00 [Molecular Neuroscience A]

Study of the interaction between phenylalanine-tRNA synthetase (FARS) and *C9orf72* antisense RNA transcripts containing C_4G_2 hexanucleotide repeats

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are related neurodegenerative diseases characterized by the accumulation of TDP-43 protein aggregates, coinciding with neuronal loss and disease progression. Although both ALS and FTD typically occur sporadically, certain genetic factors are linked to these diseases, with the most common being the expansion of G_4C_2 hexanucleotide repeats in the promoter region of the *C9orf72* gene. Currently, three main hypotheses have been proposed to explain how this genetic alteration leads to cellular pathology. According to one of these hypotheses, RNA transcripts containing C_4G_2 repeats exert toxicity by sequestering various RNA-binding proteins. A recent study identified phenylalanine-tRNA synthetase (FARS)—the enzyme responsible for charging tRNA with phenylalanine—as a key target of antisense RNA transcript. In our study, we are exploring the interaction between phenylalanine-tRNA synthetase (FARS) and antisense $(C_4G_2)_{32}$ RNA transcripts in isolated forms to uncover the molecular basis of their binding. Using size-exclusion chromatography (SEC), we found no evidence of a direct interaction between FARS and the antisense RNA, suggesting that an additional component—such as specific tRNA—may be required to bridge or stabilize the complex. A major challenge is that FARS does not effectively bind in vitro-transcribed tRNA, likely due to the lack of essential post-transcriptional modifications. To address this, we are isolating native, fully modified phenylalanine tRNA from mouse liver to assess whether it mediates FARS–RNA binding. Our ultimate goal is to isolate a stable complex and determine its structure by cryo-electron microscopy. Such insights could clarify how the most common ALS- and FTD-associated genetic mutation contributes to neuronal degeneration, providing a better understanding of the molecular mechanisms underlying these diseases.

Keywords: neurodegeneration, ALS, phenylalanin-tRNA synthetase, antisense RNA, hexanucleotide repeats

MOL.11 Thursday, September 18th, 15:00 [Molecular Neuroscience A]

Non-genetic amino acid substitutions in proteins associated with the neurodegenerative diseases amyotrophic lateral sclerosis and frontotemporal dementia

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) represent two ends of a phenotypic spectrum of a progressive and fatal neurodegenerative disease, primarily affecting motor function in ALS and cognitive and behavioural functions in FTD.

A pathological hallmark in the vast majority of ALS (97%) and FTD (60%) cases, as well as other neurodegenerative conditions, is the cytoplasmic aggregation and nuclear depletion of the otherwise nuclear protein TDP-43. TDP-43 contributes to neurodegeneration either through loss of its physiological nuclear function or through a toxic gain-of-function of its aggregates in the cytoplasm. These conditions are therefore classified as TDP-43 proteinopathies. In addition, several other RNA-binding proteins (e.g., FUS, HNRNPA1, Matrin-3) and nucleoporins (e.g., Nup62, POM121) have been implicated in ALS/FTD pathology, particularly through disruption of RNA homeostasis. However, mutations in the *TARDBP* gene encoding TDP-43 are uncommon in ALS and rare in FTD. As a result, current research increasingly explores therapeutically targetable mechanisms involving non-mutated TDP-43.

In this study, we focused on non-genetic amino acid substitutions in proteins associated with ALS and FTD that arise at the post-transcriptional, translational, or post-translational level. Using PEAKS Studio 12 proteomics software, we analysed mass spectrometry data from ALS/FTD patient and healthy control samples obtained from public repositories. We further explored the potential processes responsible for these substitutions, including mistranslation, deamidation, and RNA editing. Accordingly, we examined codon usage, focusing on rare and wobble codons that may promote mistranslation, alongside key sequence features of ALS- and FTD-associated proteins that may contribute to disease pathology.

Keywords: amyotrophic lateral sclerosis, frontotemporal dementia, proteomics, amino acid substitutions

OTH.01 Thursday, September 18th, 15:00 [Other A]

"Mind and mouth": preparation of tailored educational materials on oral health for older adults with cognitive decline

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Older adults with cognitive decline frequently experience deterioration in oral health due to reduced ability to maintain oral hygiene and coexisting medical conditions. Poor oral health represents a significant risk factor in the progression of neurodegenerative disorders. Understanding the specifics of this population group is essential for developing tailored educational materials on oral health and improving their well-being. As part of the Slovenian pilot study "Mind & Mouth" within the European COMFORTage project, which will involve 50 residents of homes for the elderly with cognitive decline, we have developed oral hygiene instructions tailored to the specific needs and characteristics of this population group. We used five key design elements: typography, colour schemes, textual content, visual elements, and layout structure. Design recommendations include sans-serif fonts in easy-to-read sizes with bold headings, high-contrast colour combinations, and simple language with short sentences and bullet points. Visual elements feature large, realistic sketches of people performing oral care tasks, avoiding abstract images. The layout maintains a clean design with white space, consistent formatting, and single concepts, accompanied by step-by-step visual guides. Combining design elements specifically tailored for older adults with cognitive decline with gamification approaches creates an engaging framework that can significantly improve motivation for oral health maintenance. This integrated approach addresses both the cognitive accessibility needs of this population while leveraging the intrinsic motivational power of game mechanics to transform routine oral care tasks into achievable, rewarding experiences that promote consistent daily practice.

Keywords: cognitive decline, elderly, oral health, tailored educational material, gamification

OTH.03 Thursday, September 18th, 15:00 [Molecular Neuroscience A]

Too much of a good fat? Lasting behavioural impact of a maternal plant-based high-fat diet on emotional and exploratory behaviour in adult female offspring

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Introduction: Studies have shown that a maternal high-fat diet (mHFD) during pregnancy and the perinatal period has been associated with various neurodevelopmental and neuropsychiatric disorders such as autism, ADHD, anxiety, depression and cognitive impairments.

Methods: Adult female Wistar rats were assigned to either the plant-based mHFD or control diet (CD). They were fed for four weeks before breeding, and the feeding continued throughout pregnancy and lactation. Following weaning, all female offspring were fed a CD, forming two groups: 1. from CD dams (FC) and 2. from HFD dams (FH). After reaching maturity, anthropometric measurements, metabolic parameters and behavioural testing were performed. The elevated plus maze (EPM) and open field test (OFT) were used to evaluate anxiety-like behaviour during the diestrus phase. The expression levels of doublecortin (DCX) and Ki-67 were measured to assess neurogenesis.

Results: FH animals had higher body weights and longer body lengths, as well as impaired glucose tolerance. In the OFT, mHFD increased locomotion and exploratory behaviour, as evidenced by increased total ambulation distance and rearing counts in the FH group. Additionally, the FH exhibited reduced anxiety-like behaviour, as shown by an increased centre ambulation distance, longer time spent in the centre, and a higher thigmotaxis index compared to the FC group. Neuronal maturation was also impaired in mHFD offspring, as seen in a lower number of KI67+ and DCX+ cells.

Conclusion: A long-term plant-based mHFD leads to increased hyperactivity and reduced anxiety in adult female offspring, which is accompanied by hindered neurogenesis and glucose intolerance.

Keywords: high-fat diet, plant-based, maternal, adhd, anxiety

OTH.05 Thursday, September 18th, 15:00 [Molecular Neuroscience A]

Comprehensive treatment of children and adolescents with special health care needs and disability (SEND)

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Objective: Children/adolescents (CA) with SEND can struggle to attend school regularly if they do not receive the right support and treatment. With genetic advancement: both testing as well as therapeutic evolution, therapy which is already individually tailored, becomes even more tailor-made.

Methods: overview of comprehensive treatment at CIRIUS Kamnik which is individually tailored.

Results: during the last school year there were 196 CA, aged 6–26 years. 107 are included in equivalent (No=38) and lower standard of primary education (23) and specific education programme (46). 87 are included in secondary education: lower vocational (22), vocational (28), a vocational engineering (17) and post-rehabilitation practicum (20). 61 CA live in institution 6/7 days. 60 have light, 30 moderate, 41 severe and 54 very severe motor impairment, which was with genetics advancement confirmed as SMA type 2 (6), muscular dystrophy (5), Prader Willi syndrome (5), individual rare disease (Apert syndrome, Down syndrome, Lesch Nyhan syndrome, CTNNB1 etc.) (100), spina bifida (4); 76 remained as CP (history of HIE, prematurity – not tested because of typical clinical phenotype and history). 11 use non-invasive ventilation and 3 invasive. They receive regular health and medical care, rehabilitation, and assessment of their needs and function (FIM, QoL, GMFM, MoCA).

Conclusions: Multidisciplinary approach offers better quality of life and enable integration into society because of healthcare integrated into school system. Their therapy is individually tailored, however, with genetic advancement and development of rare disease therapies, the pressure to offer it to everyone has grown immensely. As clinicians we need clearer understanding of who should be genetically tested; how can we differentiate between monogenic causes and i.e.: CP risk factors; also logistics and costs of both testing (gatekeeping) and therapy (clinical utility) should be considered.

SYS.01 Thursday, September 18th, 15:00 [Systems Neuroscience A]

Differential effects of R- and S-ketamine in Wistar-Kyoto rats: implications for treatment-resistant depression

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Ketamine, a fast-acting antidepressant, has shown promise for treatment-resistant depression (TRD). It exists as two enantiomers, R- and S-ketamine, with preclinical studies suggesting greater efficacy and fewer side effects with R-ketamine. However, many of these studies use acute or short-term protocols, limiting their translational relevance. This study aimed to assess the effects of repeated administration of ketamine enantiomers in Wistar-Kyoto (WKY) rats, a model of TRD, and Wistar (W) control rats, using a protocol that more closely resembles long-term clinical treatment. Adult male WKY and W rats received repeated subcutaneous injections of saline, R-ketamine, or S-ketamine. We evaluated psychomotor effects, depressive-like behavior, and neuroplastic changes. S-ketamine induced stronger psychomotor effects, including locomotor stimulation, ataxia, and stereotypy, than R-ketamine. WKY rats were more sensitive to these effects. Repeated administration led to locomotor sensitization and tolerance to ataxia. Increased c-Fos and ΔFosB expression was observed in the retrosplenial cortex after S-ketamine. Wistar rats showed higher ΔFosB levels than WKY rats across the prefrontal cortex, nucleus accumbens, and hippocampus. No antidepressant-like effects or other neuroplastic changes were found. In conclusion, S-ketamine produced stronger psychomotor and molecular effects than R-ketamine, and WKY rats were more behaviorally sensitive. Our results indicate that depressed patients may be more sensitive to ketamine's psychomotor side effects, with repeated use potentially altering tolerability and treatment experience over time.

Keywords: ketamine, depression, rapid antidepressant, preclinical, psychomotor

CEL.02 Friday, September 19th, 15:15 [Cellular Neuroscience B]

Neuroprotective role of γ-enolase in cellular models of Alzheimer's and Parkinson's disease

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Alzheimer's disease (AD) and Parkinson's disease (PD) involve progressive degeneration of cholinergic and dopaminergic neurons, respectively, underscoring the need for targeted neuroprotective strategies. γ-Enolase, a neuron-specific glycolytic enzyme, also exerts neurotrophic functions essential for neuron survival and differentiation. These effects depend on its intact C-terminal region, which is proteolytically cleaved by cathepsin X, thereby diminishing its protective potential. This study investigated the neuroprotective role of γ-enolase and the regulatory impact of cathepsin X using differentiated SH-SY5Y cells as *in vitro* neuronal models relevant to AD and PD. In the AD model, cholinergic differentiation was induced by retinoic acid and brain-derived neurotrophic factor, followed by exposure to amyloid-β (Aβ). The expressed full-length γ-enolase promoted neurite outgrowth and expression of cholinergic markers, while its C-terminally truncated form impaired neuronal maturation. Aβ exposure decreased the level of active form of γ-enolase and cell viability. These effects were reversed by the cathepsin X inhibitor AMS36, which preserved cytoskeletal integrity and improved survival. In the PD model, dopaminergic differentiation was achieved by retinoic acid and phorbol 12-myristate 13-acetate, followed by treatment with 6-hydroxydopamine. Toxin exposure decreased the level of γ-enolase, altered its subcellular localization and increased apoptosis. AMS36 or a synthetic C-terminal γ-enolase peptide restored γ-enolase active form level, reduced cell death and maintained the neuronal integrity. These results indicate that regulation of γ-enolase by cathepsin X is a promising therapeutic target. Preserving γ-enolase activity may offer a disease-modifying strategy to protect vulnerable neurons in AD and PD.

Keywords: γ-enolase, cathepsin X inhibition, neuroprotection, Alzheimer's disease, Parkinson's disease

CEL.04 Friday, September 19th, 15:15 [Cellular Neuroscience B]

Astrocytes as primary responders to neuromodulatory octopaminergic calcium signals in the *Drosophila* brain

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Octopamine in the *Drosophila* brain plays a neuromodulatory role analogous to noradrenaline in mammals. Released from Tdc2-expressing neurons, octopamine and tyramine act via G protein-coupled adrenoceptor-like receptors, octopamine (OctR) and tyramine (TyrR) receptors, on neural cells, modulating intracellular Ca^{2+} signaling and neurotransmission. Although these receptors are expressed in both neurons and glia, cell type-specific responses to octopaminergic signals remain poorly defined.

To address this, we expressed the genetically encoded Ca^{2+} indicator jGCaMP7b in specific cell types of adult *Drosophila* brains and used confocal microscopy to monitor Ca^{2+} dynamics in the optic lobes during bath application of octopamine. Octopamine induced distinct Ca^{2+} responses in neurons and astrocytes. Neuronal responses were characterized by Ca^{2+} transients with amplitudes 3.4-fold higher than those in astrocytes. In contrast, astrocytes displayed higher sensitivity, responding to nearly six-fold lower octopamine concentrations. Pharmacological inhibition of α1- and β-adrenoceptor homologues with selective antagonists reduced octopamine-evoked Ca^{2+}r esponses in both cell types, suggesting the involvement of both G_q/Ca^{2+} and G_s/cAMP signalling pathways. Single-nucleus RNA sequencing (snRNA-seq) data screening revealed cell type-specific expression of OctR and TyrR receptors, supporting the observed functional differences in signaling.

Notably, only astrocytes responded to low concentrations of octopamine in the optic lobes, identifying them as the primary sensors of octopaminergic signaling in this region. These findings highlight a central role for optic lobe astrocytes in modulating synaptic plasticity and visual processing. Given the integration of the optic lobes with higher brain centers such as the mushroom body, astrocyte-driven octopaminergic signaling may also influence neural activity underlying cognitive processes like learning and memory.

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CEL.06 Friday, September 19th, 15:15 [Cellular Neuroscience B]

Regulation of second messenger dynamics and mechanosensitivity in 3T3 cells and astrocytes by the orphan receptor GPR27

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GPR27 is an orphan receptor and belongs to a family of super-conserved receptors expressed in the brain (SREB)[1]. GPR27 appears to play a role in insulin production[2], lipid metabolism[3] and is also involved in L-lactate homeostasis (LL). It has been shown that GPR27 stimulation enhances aerobic glycolysis (AG) and LL production in NIH-3T3 MEF cells and primary rat cortical astrocytes[4]. Here, we investigated whether activation of the GPR27 receptor by GPR27 surrogate agonist (1 μM) involves signalling via the second messengers Ca^{2+} and cAMP. We used a Förster resonance energy transfer (FRET)-based cAMP nanosensor to monitor cytosolic cAMP with high temporal resolution in single cells. Intracellular Ca^{2+} was monitored with Ca^{2+}indicator Calbryte 520AM in real time. Our preliminary results show that stimulation of GPR27 with a surrogate agonist increases $[Ca^{2+}]_i$ but not $[cAMP]_i$ in WT 3T3 cells. In astrocytes, the GPR27-surrogate agonist also caused an increase in $[Ca^{2+}]_i$. We have observed that GPR27 modulates $[cAMP]_i$ responses following L-lactate stimulation in 3T3 cells. Interestingly, in control experiments, we also observed an increase in $[cAMP]_i$ in both 3T3 cells and astrocytes in response to the addition of vehicle (extracellular solution). In 3T3 cells with CRISPR-Cas9 GPR27 knockout, the vehicle-induced increase in $[cAMP]_i$ was greater than WT controls. Transfection of GPR27KO 3T3 cells with a plasmid encoding GPR27 attenuated the vehicle-induced increase in $[cAMP]_i$. Additionally, we observed that the addition of vehicle also induced an increase in $[Ca^{2+}]_i$ in GPR27KO 3T3 cells. Previous studies of mechanosensitive signalling in mouse and rat astrocytes have suggested the possible involvement of mechanically activated channels, including PIEZO channels[5] and most notably TRPV4 channels[6]. We observed that both TRPV4 and Piezo1 channels are more abundantly expressed in GPR27KO 3T3 cells, which could explain the observed responses after vehicle stimulation. It appears that GPR27 not only plays a role in AG and LL production but is also likely involved in the mechanosensitivity of cells.

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CLI.02 Friday, September 19th, 15:15 [Clinical Neuroscience B]

Individual differences in global brain connectivity changes after rTMS for depression: an exploratory study

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Repetitive transcranial magnetic stimulation (rTMS) is an established treatment for treatment-resistant depression, yet therapeutic outcomes vary considerably between individuals. Increasing evidence suggests that major depressive disorder (MDD) is not a uniform condition, but rather a heterogeneous constellation of symptom clusters with distinct neurobiological underpinnings. In this exploratory study, we examined the neural effects of rTMS using resting-state functional MRI (RS-fMRI) of 24 patients with MDD acquired before and after treatment. We computed global brain connectivity (GBC) maps for each patient at both time points and calculated individual-level change maps (ΔGBC = RSpost − RSpre). Using these data, we applied hierarchical clustering using Ward's method and identified two distinct subgroups characterized by divergent patterns of GBC change. One cluster showed alterations associated with motor areas, while the other exhibited changes in fronto-parietal regions typically associated with cognitive control networks. These findings align with existing work suggesting the presence of biological subtypes in major depression. Although our results are preliminary (and descriptive in nature), they highlight the importance of considering individual variability in brain network reorganization following rTMS. Future research should investigate whether these connectivity patterns correlate with specific symptom improvements, e.g., whether motor-related GBC changes predict improvement in psychomotor symptoms of depression, or whether fronto-parietal changes relate to cognitive-affective recovery. Understanding such relationships could guide the development of personalized rTMS interventions and improve targeting strategies based on pre-treatment connectivity profiles or symptom dimensions. Our findings contribute to the growing effort to tailor neuromodulation treatments to individual patients based on neurofunctional markers.

Keywords: rTMS, major depressive disorder, functional brain connectivity, connectivity-based clustering, personalized treatment

CLI.04 Friday, September 19th, 15:15 [Clinical Neuroscience B]

The psychological situation of family caregivers of relatives with dementia

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Approximately 80% of individuals with dementia are cared for by family members, often under high emotional, physical, and psychological demands. These family caregivers (FCGs) are at increased risk of anxiety, depression, social isolation, and diminished quality of life. This doctoral study, grounded in the Caregiver Stress Model, aims to examine the psychosocial and physiological burden of Portuguese family caregivers (PFCGs). Using a cross-sectional design, 1,310 caregivers will be recruited from hospitals, care homes, and Alzheimer's associations. Participants will complete a psychometric battery including the HADS, WHOQOL, PSQI, Brief COPE, and MSPSS. A voluntary sub-sample will provide biological stress markers—interleukin-6 (IL-6), C-reactive protein (CRP), cortisol, homocysteine, cholesterol, and blood pressure.It has been shown that GPR27 stimulation enhances aerobic glycolysis —to evaluate physiological responses to chronic caregiving stress. The study assumes a complex interaction between caregiving demands, individual coping mechanisms, and access to social support, which together influence mental and physical health outcomes. We hypothesize that higher caregiving burden will be associated with poorer psychosocial well-being and elevated inflammatory markers, moderated by personal and contextual factors. The findings aim to advance the theoretical understanding of caregiver stress and support the development of targeted, evidence-based interventions. This research is expected to inform socially responsive public health strategies and policies that address the real needs of dementia caregivers, an essential but often overlooked population.

Keywords: dementia, caregiver stress model, family caregivers, chronic stress, biological markers

CLI.06 Friday, September 19th, 15:15 [Clinical Neuroscience B]

Twins with dystonic diparesis: is it CP or is it CTNNB1 mutation?

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Objective: CTNNB1 Syndrome is rare genetic neurodevelopmental disorder caused by pathogenic variants in the CTNNB1 gene. Diagnosis is made through genetic testing (WGS, trio exome). We present clinical reasoning which led to CTNNB1 diagnosis.

Methods: We present twins with cerebral palsy (CP) which was attributed to prematurity (31 weeks of GS) and HIE grade 2. Gemini A had PFO and VSD which closed spontaneously and bilateral PVL described upon MR, while gemini B had PFO which closed spontaneously, bilateral PVL, including the occipital lobe; he also developed hyaline membrane disease. In adolescence, clinical picture deteriorated: cognitive impairment and communication difficulties became more obvious, spasticity in legs led to contractures which were surgically resolved, walking abilities deteriorated. While questionnaires (QoL: SF36v2, GMFCS, GMFM, MOCA, BMFM and MACS) stayed the same, we observed deterioration in FIM from 101/126 and 99/126 to 92/126 and 88/126 in gemini A and B. In addition, we have received genetic results of mother, who has the ASXL3 mutation (Bainbridge-Ropers syndrome) which was discovered during testing for SCN1A mutation (Dravet syndrome), which was discovered in 3 of her daughters (half-sisters of twins). Neurodegeneration, specific phenotype (including walking, axial hypotony, limb spasticity, dystony, microcephaly, cognitive impairment), and specific genetic situation led us to screen for genetic causes of CP.

Results: In both twins *de novo* pathogenic heterozygous variant with reading frame shift in gene CTNNB1 (NM_001904.4:c:688dup, p.Ala230Glyfs*4) was found, which was not yet reported. However, it was found near ClinVar pathogenic variant with reading frame shift (c.696del and c.705dup).

Conclusions: As long as all children with CP do not receive genetic testing, specialist with neurological background knowledge and access to WGS (trio exome) should consider genetic testing in children with specific features. As in described cases, genomic testing increases the risk of incidental findings, which can lead to considerable distress for families and can be time-consuming and complex to explain.

COG.02 Friday, September 19th, 15:15 [Cognitive Neuroscience B]

Emotion regulation strategies in healthy young adults: a multimodal psychophysiological investigation

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Emotion regulation is essential for successful adaptation to a dynamic and unpredictable environment, with impairments in this capacity closely linked to the development and maintenance of various forms of psychopathology. Although emotion regulation has been extensively studied, past investigations have predominantly relied on subjective reports of emotional experience. In contrast, psychophysiological measures have been examined with less coherence, limiting a comprehensive understanding of how different regulation strategies influence emotional responses. To address this gap, the present study examined the effects of four commonly used emotion regulation strategies - distraction, reappraisal, distancing, and suppression - on subjective, autonomic, and neural indicators of emotional reactivity. A sample of 61 healthy undergraduate students (aged 19–20) completed an emotion regulation task involving emotionally evocative stimuli while employing previously trained emotion regulation strategies. Emotional responses were assessed through self-reported valence and arousal ratings, autonomic nervous system measures (heart rate, respiration, pupil dilation, electrodermal and electromyographic activity), and EEG activity.

This multimodal approach enabled us to evaluate the coherence and divergence of emotional response patterns across different regulation strategies and measurement modalities. Preliminary findings indicate that the strategies differentially modulate emotional responses, with distinct effects observed across subjective, autonomic, and EEG outcomes. These results underscore the importance of integrating multiple levels of analysis in the study of emotion regulation and highlight the need for greater methodological rigor in psychophysiological research on this topic.

Keywords: emotion, emotion regulation, psychophysiology, multimodal assessment

COG.04 Friday, September 19th, 15:15 [Cognitive Neuroscience B]

Subclinical anxiety is associated with reduced self-distancing and enhanced guilt-related connectivity between anterior temporal and subgenual cingulate cortex

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Excessive self-blaming emotions are a hallmark of anxiety disorders, with mounting evidence indicating the presence of qualitatively similar symptomatology in subclinical and clinical populations. We previously pinpointed the central role of the superior anterior temporal lobe (sATL) in the guilt processing circuitry, together with network organisation differences associated with subclinical anxiety. This study aimed to extend these findings by exploring links of anxiety with self-blaming emotions and associated behaviours, guilt-dependent neural activity and connectivity, and the role of resting-state fMRI in linking these phenomena. Increased anxiety was linked to stronger self-blaming emotions, and more pronounced self-attacking and hiding. When experiencing negative emotions about themselves, i.e. shame and self-anger, anxious individuals were also less likely to disengage from self-focused cognitions. These behavioural findings were paralleled by enhanced guilt-related connectivity between the left sATL and subgenual cingulate cortex. The relevance of ATL activity and its increased connectivity with guilt processing regions for self-blaming emotions and anxiety was further hinted by the resting-state analysis. Interestingly, while approach-avoidance motivation of guilt memories was unrelated to anxiety, this dimension of emotional experiences showed distinct contributions of the left and right sATL, with the normative maps of dopaminergic and serotonergic molecules density suggesting their potential role in the process. As such, the results of the current study link the self-blaming bias of anxious individuals to specific maladaptive patterns of behaviour. Furthermore, the work provides robust evidence for the important role of sATL-related circuitry in guilt processing, simultaneously highlighting the complex, multidimensional nature of the phenomenon.

Keywords: anxiety, guilt, self-blame, approach-avoidance motivation, fMRI

MOL.02 Friday, September 19th, 15:15 [Molecular Neuroscience B]

Heightened risk of tau pathology onset following SARS-CoV-2 infection

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The goal of this study is to investigate the long-term effects arising from the infection of various SARS-CoV-2 strains on the brain. As previously discovered, there is a strong interplay between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and neurodegenerative events, particularly those related to Alzheimer's disease. Specifically, we have demonstrated that acute SARS-CoV-2 infection leads to phosphorylation of Tau at several pathological epitopes associated with Alzheimer's disease and other tauopathies. This modification increases the propensity for Tau delocalization and the subsequent formation of insoluble aggregates. At present, our efforts are directed toward long covid study and effect on the brain. Both the molecular aspects as well as the functional outcomes such as the solubility aggregation and the cognitive impairment have been evaluated on infected murine models up to 90 days post-infection (dpi). Preliminary results with both the Wuhan and the Delta variants demonstrate a behavioural recovery at 90dpi compared to 30dpi. Surprisingly, Western blot analyses of brains at 90dpi reveal a substantial presence of Tau, including phosphorylated forms at pathological epitopes, in the insoluble fraction. These results indicate that although brain fog is no longer observed long after infection, pathological forms of tau persist in the brain, suggesting a potential predisposition to long-term cognitive impairment.

Keywords: SARS-CoV-2, tau, aggregation, cognitive impairment, Alzheimer's disease

NTRK3 as a mediator of neuronal differentiation in sonic hedgehog pathway-activated medulloblastoma

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Sonic Hedgehog pathway-activated medulloblastoma (SHH-MB) is an aggressive pediatric brain tumor with therapeutic standards that provide only limited long-term control. A deeper understanding of tumor biology is essential for identifying novel therapeutic targets and developing effective therapies. Using single-cell RNA sequencing (scRNAseq), we identified two dominant malignant cell populations in SHH-MB, including proliferative stem cell-like and neuron-like cells.

Our preliminary scRNAseq data suggest that these cell populations communicate via receptor-ligand interactions. We identified a significant overexpression of Neurotrophin receptor tyrosine kinase 3 (NTRK3), encoding the TRK-C receptor, in the stem cell-like SHH-MB cells, suggesting a key in neuronal differentiation.

To evaluate the functional relevance of NTRK3 signaling in SHH-MB, we utilized the TRK-C-targeting small-molecule inhibitor entrectinib, NT3 ligand stimulation, and siRNA-mediated knockdown in SHH-MB cell models. Subsequently, we performed cell viability, tumor spheroid cytotoxicity, invasion assays, and qRT-PCR. After 24 hours of TRK-C inhibition, we identified significantly decreased stem-like cell markers (NTRK3, SERPINF1), while neuronal differentiation markers (NEUROD1, ERBB4, SOX11) showed a significant increase. In functional experiments, we observed that entrectinib significantly impaired tumor spheroid invasion into Matrigel, while ligand stimulation increased invasive capacities. Furthermore, both entrectinib and NTRK3 knockdown exhibited significant cytotoxic effects and impaired cell viability in the low micromolar range in SHH-MB cells.

Our findings demonstrate that NTRK3 is a crucial mediator of neuronal differentiation and potentially contributes to oncogenic signaling in SHH-MB. Targeting the NTRK3 signaling pathway represents a promising strategy for therapeutic intervention.

Keywords: NTRK3, neuronal differentiation, SHH-MB

Small RNAs regulate TDP-43 aggregation

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Neuronal cytoplasmic aggregates of TDP-43 represent the most common pathological hallmark in nearly all cases of amyotrophic lateral sclerosis (ALS) and approximately half of frontotemporal dementia (FTD) cases. Aggregation is typically accompanied by loss of nuclear TDP-43, but whether disease arises from a toxic gain or loss of function remains unresolved. TDP-43 is an RNA- and DNA-binding protein that regulates multiple steps of RNA metabolism. Under physiological conditions, it is primarily nuclear, though it dynamically shuttles between the nucleus and cytoplasm. Our work focuses on the largely unexplored interactions between TDP-43 and cytoplasmic structural small RNAs. Reanalysis of crosslinking and immunoprecipitation (CLIP) data identified TDP-43 binding to multiple tRNAs and all known YRNAs. Selected interactions were confirmed and quantified using microscale thermophoresis (MST), demonstrating strong binding affinities. *In vitro* aggregation assays showed that these interactions suppress TDP-43 aggregation, with the extent of inhibition increasing in a concentration-dependent manner. An in vitro-transcribed tRNA derived from one of the top CLIP hits exhibited even greater inhibitory effects. Aggregation samples were further examined by light microscopy.

Keywords: TDP-43, small RNAs, aggregation assay, ALS, FTD

MOL.08 Friday, September 19th, 15:15 [Molecular Neuroscience B]

ORF1p nuclear import mechanism revealed: a step toward understanding LINE-1 in neurons

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Long interspersed nuclear element-1 (LINE-1) is the only active autonomous retrotransposon in the human genome. This study investigates the mechanism underlying the nuclear import of LINE-1 open reading frame 1 protein (ORF1p), a necessary step for retrotransposition. ORF1p has been detected in non-dividing cells such as neurons, where its accumulation and activity are associated with genomic instability, inflammation, and neuronal dysfunction—hallmarks of neurodegenerative diseases such as ALS and FTD. However, the specific pathway by which ORF1p translocates across the nuclear envelope in post-mitotic neurons remains undefined, representing a key gap in our understanding of LINE-1–driven neurotoxicity. To address this, we performed a nuclear import assay (NIA) using recombinant proteins expressed and purified from Escherichia coli: ORF1p, Ran GTPase, and a panel of candidate karyopherins. The NIA was carried out using digitonin-permeabilized HeLa cells, to which an import mix containing ORF1p, nuclear import factors, and an ATP-regenerating system was added. First, we included rabbit reticulocyte lysate in the import mix to enable nuclear import. Under these conditions, ORF1p accumulated in nuclei, confirming that its import is a karyopherin-dependent active transport process. Next, to identify the specific transport receptors involved, we replaced the lysate with individual purified karyopherins. We showed that ORF1p can be imported by specific karyopherin α/β complexes, indicating that ORF1p is actively transported through the nuclear pore complex. Given LINE-1's role in neurodegenerative diseases, targeting ORF1p's nuclear import pathway may offer a new strategy for modulating retrotransposon-driven pathologies in neurons.

Keywords: LINE-1, ORF1p, nuclear import, neurons, neurodegenerative disease

MOL.10 Friday, September 19th, 15:15 [Molecular Neuroscience B]

Highly sensitive detection of cytoplasmic antisense *C9orf72* repeat RNA via RNA–RNA proximity ligation assay

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are neurodegenerative diseases frequently linked to a pathogenic expansion in the *C9orf72* gene. This expansion involves a GGGGCC hexanucleotide repeat that is transcribed in both the sense $(G_4C_2)_n$ and antisense $(C_4G_2)_n$ directions, forming RNA foci predominantly in the nucleus. While these nuclear aggregates have been extensively characterized, the potential presence and localization of these toxic RNA repeats in the cytoplasm remains underexplored, due in part to the limited sensitivity of conventional detection methods such as fluorescence in situ hybridization (FISH). We applied an optimized RNA-RNA proximity ligation assay (RNA-RNA PLA) to visualize the antisense *C9orf72* repeat transcripts with high spatial resolution and sensitivity. By utilizing biotinylated locked nucleic acid (LNA) probes in combination with anti-biotin antibodies and PLA probes, we successfully detected distinct cytoplasmic antisense repeat signals in patient-derived cells; signals that are often missed by FISH. Protocol refinements, including increased tRNA blocking and modified antibody dilutions, significantly improved specificity and reduced background staining. These improvements enabled clear differentiation between mutant and control samples. Our results highlight RNA-RNA PLA as a powerful tool to detect low-abundance, spatially dispersed RNA species such as antisense *C9orf72* repeats. The ability to observe these transcripts outside the nucleus may have important implications for understanding RNA toxicity mechanisms and guiding the development of targeted therapeutics.

Keywords: *C9orf72* repeat expansion, RNA RNA proximity ligation assay (PLA), cytoplasmic RNA foci, ALS/FTD

MOL.12 Friday, September 19th, 15:15 [Molecular Neuroscience B]

Interplay between LINE-1 and YRNAs: interaction and retrotransposition

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LINE-1 (Long Interspersed Nuclear Element-1) is the only autonomous retrotransposon in humans, accounting for up to 17% of the genome. Studies have linked increased levels of LINE-1 retrotransposition and its dysregulation to various neurodegenerative diseases, where aberrant LINE-1 activity is associated with genomic instability, cellular dysfunction, and inflammation. To better understand how LINE-1 activity is regulated in cells, we investigated a LINE-1–encoded protein called ORF1p. ORF1p is an RNA-binding protein that functions as a nucleic acid chaperone; however, its interacting partners remain poorly characterized. By performing iCLIP, we discovered that ORF1p interacts with a group of non-coding RNAs known as Y RNAs. Of the four YRNAs expressed in humans, iCLIP revealed the highest number of cross-linking events with RNY1, RNY3, and RNY4. Interestingly, all cross-linking events in RNY4 mapped to a specific region in the lower stem, indicating a precise and potentially functional interaction between ORF1p and RNY4, warranting further investigation. We first confirmed the interaction between ORF1p and RNY4 *in vitro* using a pull-down assay. Next, we explored the effect of RNY4 on LINE-1 retrotransposition levels. To this end, we overexpressed RNY4 in HeLa and HEK293T cells and performed a retrotransposition assay. Flow cytometry analysis demonstrated that RNY4 inhibits LINE-1 retrotransposition in both cell lines, reducing retrotransposition levels by approximately 25%. These findings clearly demonstrate an interplay between LINE-1 and YRNAs, highlighting a previously unrecognized regulatory mechanism that warrants further study.

Keywords: LINE-1, ORF1p, YRNA, neurodegenerative diseases

OTH.02 Friday, September 19th, 15:15 [Other B]

Salicylic acid surface modification reduces TiO_2 nanoparticle-induced lipid peroxidation in rat brain tissue

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Titanium dioxide nanoparticles (TiO_2 NPs) are widely used in food, pharmaceuticals, cosmetics, paints, and other industries. However, growing evidence has raised concerns about their potential neurotoxic effects, which may depend on particle size, shape, dose, and route of exposure. As surface modification emerges as a promising strategy to reduce TiO_2 toxicity, the aim of our research was to compare the effects of bare, commercially available TiO_2 NPs and TiO_2 NPs surface-modified with salicylic acid (SA/TiO2 NPs) in adult female Wistar rats. Rats (n=12) received single oral treatment of either vehicle (2.5 mL 0.01 M HCl), TiO_2 NPs or SA/TiO_2 NPs (1000 mg/kg suspended in vehicle). Two weeks post-treatment, the animals were sacrificed, brain tissue was collected, and oxidative stress parameters were analyzed in the crude synaptosomal (P2) fraction. The prooxidant–antioxidant balance (PAB) level was significantly increased in TiO_2 NPs-treated group compared to vehicle, indicating oxidative stress induction. Levels of advanced oxidation protein products (AOPP) did not differ significantly between groups. However, lipid peroxidation (LPO) was markedly elevated in TiO_2 NPs group, while SA modification effectively restored LPO to levels observed in vehicle. Our findings suggest that surface modification of TiO_2 NPs with SA reduces toxic prooxidative effect manifested via attenuation of LPO levels in brain tissue. This approach offers a promising direction for enhancing nanoparticle biocompatibility, however, further studies are needed to clarify underlying mechanisms and explore alternative modifications with improved protective potential.

Keywords: titanium dioxide nanoparticles, surface modification, oxidative stress, Wistar rat

OTH.04 Friday, September 19th, 15:15 [Other B]

Bridging the generational communication gap through digital and cognitive interventions for active ageing

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The growing communication gap between generations has important psychosocial implications, including loneliness, prejudice, and social exclusion. One key factor is the digital illiteracy of older adults, which often which often limits their participation in the digital world. The *Poveži se* project, grounded in the biopsychosocial model of ageing, addresses this challenge through the development and implementation of integrated interventions that promote intergenerational communication, digital literacy, and cognitive functioning among older adults.

A special emphasis is placed on learning how to effectively communicate with older adults when introducing them to digital tools, ensuring that technology serves as a support rather than a barrier. Interventions combine the use of serious cognitive games, smart devices, and tablets with cognitive-behavioral strategies, neuroimaging techniques, and intergenerational workshops in institutional environments.

Participants gain practical experience in intergenerational teaching, with the goal of enabling older adults to independently use digital tools. The intervention seeks to enhance the sense of competence in teaching, while empowering older adults in their use of digital tools and motivating them to continue engaging with digital content. It also encourages social interaction and fosters older adults' confidence and engagement in cognitively demanding tasks especially among those experiencing mild cognitive decline.By integrating practical, ethically grounded solutions with current knowledge on ageing and cognition, the project's result offers a holistic model for further use on how to foster social cohesion and active ageing through meaningful intergenerational engagement and digital empowerment.

Keywords: intergenerational communication, biopsychosocial model, digital literacy, serious games, neuroimaging

OTH.06 Friday, September 19th, 15:15 [Other B]

Getting ETHAI-cal: a framework for responsible AI in healthcare

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Artificial intelligence (AI) is rapidly transforming healthcare through predictive diagnostics, personalized interventions, and pattern recognition in large datasets. However, without ethical safeguards and contextual awareness, AI risks perpetuating bias, misunderstanding patients, and producing ineffective outcomes. We present two studies illustrating these risks. First, we modelled rehabilitation trajectories in post-stroke patients based on brain connectivity data. In the second, we analysed cognitive performance in older adults with dementia in relation to oral health parameters. While both yielded statistically significant results, the first illustrated that misunderstanding how models learn produces misleading conclusions, and the second showed the importance of interpreting model outputs in a wider context, not missing the forest for the trees.

To address these concerns, we propose incorporating ETHAI, a structured design methodology for developing ethically aligned AI, devised by CyberEthics Lab, within healthcare research projects(1). We present how ETHAI works, integrating continuous stakeholder engagement, ethical foresight, and interdisciplinary co-design throughout the development lifecycle, through the experience of using it in the COMFORTage project to explore connections between oral health, cognition and well-being. ETHAI emphasizes transparency in model assumptions, iterative evaluation with experts, and formal bias auditing tools. Preliminary results show that applying ETHAI principles improves alignment between model outputs and real-world decision-making, particularly in interpretability and clinical relevance of results. Our findings underscore that by making ethics integration a core requirement for AI in healthcare, instead of an afterthought, ETHAI provides a replicable roadmap for translating biomedical research into responsible, patient-centred solutions.

(1) EU funded MESCoBraD and COMFORTage projects.

Keywords: artificial intelligence, ethics, healthcare, cognition

SYS.02 Friday, September 19th, 15:15 [System Neuroscence B]

Anhedonia in rat model of treatment-resistant depression: insights from ultrasonic vocalizations and related behavioral measures

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The Wistar-Kyoto rat line (WKY) is a widely used model for treatment-resistant depression, exhibiting behavioral and neurochemical features consistent with the anhedonic phenotype. This study aimed to detect whether 50-kHz ultrasonic vocalizations (USVs) in response to pharmacological appetitive stimuli provide additional information about anhedonia in WKY rats. 50-kHz calls were taken as a measure of hedonic arousal and compared between WKY and Wistar (W) rats in a protocol following repeated exposure to two appetitive stimuli: amphetamine (AMPH) and morphine (MORPH). Additional behavioral measures of hedonic arousal were collected: the drug-evoked test of locomotor activity, sucrose consumption in the sucrose preference test (SPT), and approach behavior in the conditioned place preference (CPP) test. SPT was carried out twice, before and after repeated treatments with AMPH or MORPH. WKY rats consistently produced fewer 50-kHz calls across all conditions. Contrary to controls, AMPH affected 50-kHz calls in the WKY rats only after repeated treatment, suggesting diminished and delayed hedonic arousal. WKY rats also displayed reduced AMPH-induced locomotor activity and sucrose consumption in the SPT. AMPH-induced locomotor stimulation was present from the start in WKY rats, suggesting physiological arousal. Sensitization occurred in both strains after repeated treatment. MORPH did not affect 50-kHz calls or locomotion in either strain. AMPH or MORPH CPP did not occur. These results highlight 50-kHz calls as a sensitive and complementary behavioral marker for assessing anhedonia in preclinical models of depression.

Keywords: ultrasonic vocalizations, Wistar-Kyoto rat, anhedonia

SYS.04 Friday, September 19th, 15:15 [System Neuroscence B]

The role of the medial prefrontal cortex in a short- and long-term spatial memory task in mice

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AThe medial prefrontal cortex (mPFC) is involved in numerous cognitive functions, including memory processing. Spatial memories are thought to initially be encoded in the entorhinal-hippocampal circuit, and consecutively be transferred into the cortex via memory consolidation. In the mPFC, space is represented in an abstract form, as opposed to the spatial representation by so-called place cells in the hippocampus. A substantial proportion of mPFC cells exhibits activity related to rewards and reward expectancy.

Our work aims to understand the prefrontal involvement in a spatial short- and long-term memory task in mice. We examine at what stage place-related activity emerges in relation to the spatial learning, and test whether reward locations are disproportionally represented in the mPFC at different times. For this we perform extracellular recordings in the prelimbic area of the mPFC in freely moving mice with permanently implanted arrays of movable tetrodes. Electrophysiological and positional data is collected throughout the entire learning phase, and short- and long-term memory retrieval phases of an adapted cheeseboard task.

Keywords: prefrontal cortex, spatial memory, mice

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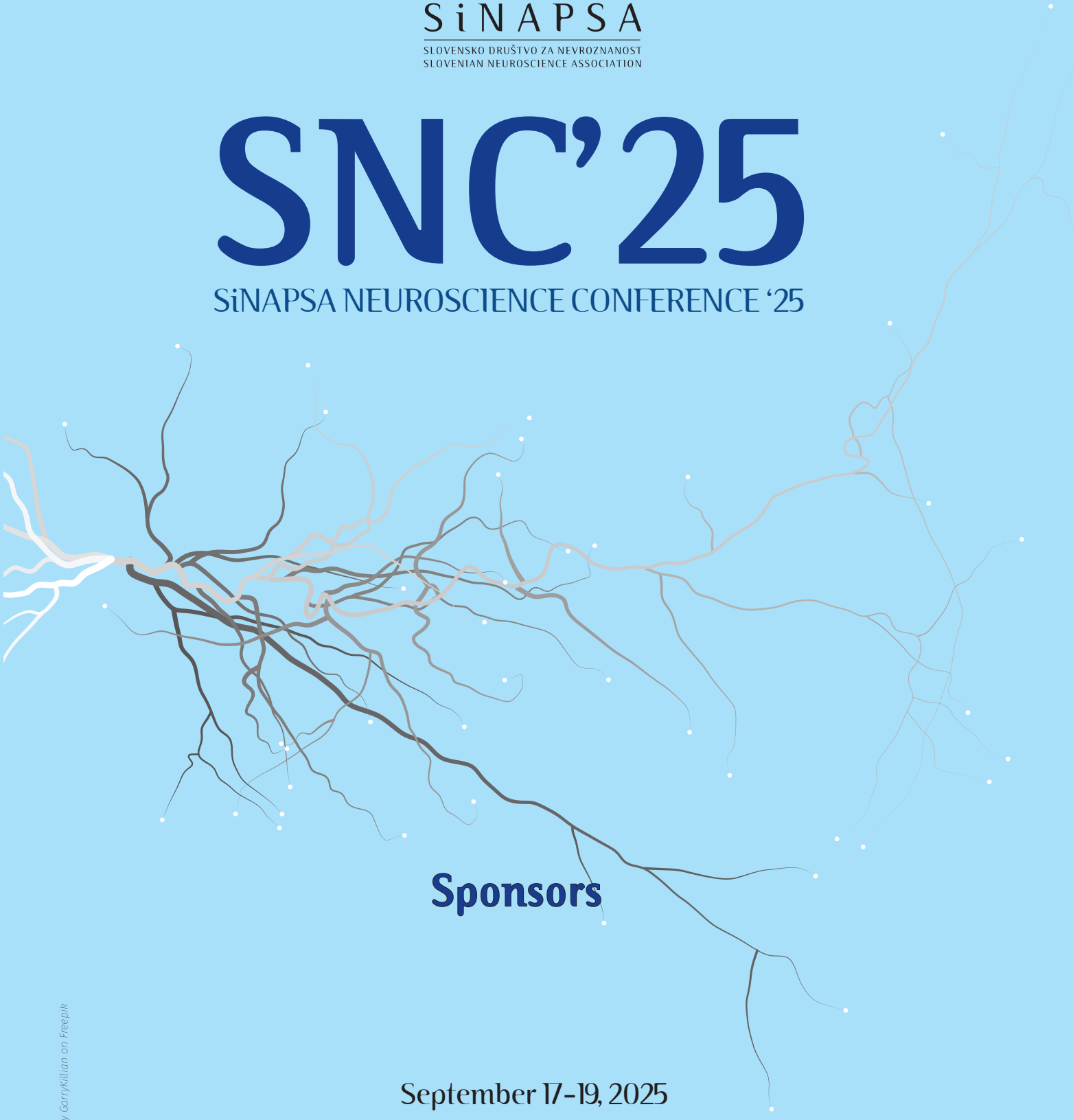

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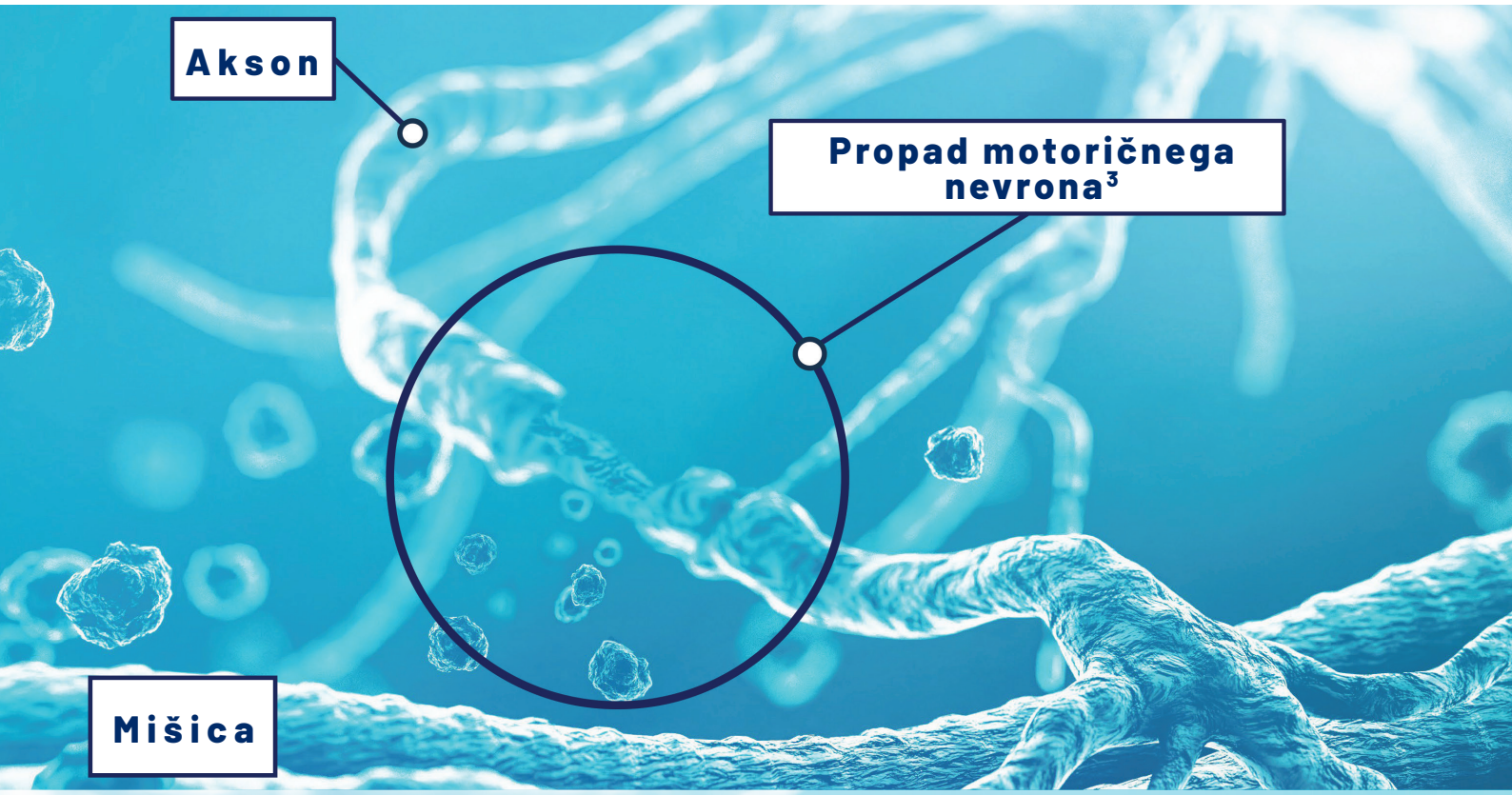

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Reference: 1. Povzetek glavnih značilnosti zdravila Qalsody, julij 2024 **2.** Akçiman F, et al. Nat Rev Genet 2023;24(9):642-658. **3.** Thompson AG, et al. Brain Commun 2022; https://doi.org/10.1093/braincomms/fcac029 **4.** Rinaldi C, Wood MJ. Nat Rev Neurol. 2018;14:9-21. **5.** Bennett FC, et al. Annu Rev Neurosci. 2019;42:385-406

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8 Povzetka glavnih značilnosti zdravila Qalsody, kako poročati o neželenih učinkih.

Skrajšan povzetek glavnih značilnosti zdravila Qalsody: Ime zdravila: ▼Qalsody 100 mg raztopina za injiciranje • **Sestava:** En ml vsebuje 6,7 mg tofersena. • **Terapevtske indikacije:** Zdravljenje odraslih z amiotrofično lateralno sklerozo (ALS), povezano z mutacijo v genu za superoksid dismutazo 1 (SOD1). • **Odmerjanje:** Zdravljenje s tofersenom sme začeti le zdravnik, ki ima izkušnje z zdravljenjem ALS. Zdravilo smejo dajati samo zdravstveni delavci z izkušnjami pri izvajanju lumbalnih punkcij ali drugi pod njihovim nadzorom. Priporočeni odmerek je 100 mg tofersena na zdravljenje. Zdravljenje s tofersenom je treba začeti s 3 polnilnimi odmerki, ki se dajejo v 14-dnevnih presledkih. Vzdrževalni odmerek je treba nato dajati enkrat na vsakih 28 dni. Če drugi polnilni odmerek zamudite ali ga izpustite, je treba tofersen uporabiti čim prej, tretji polnilni odmerek pa je treba dati čez 14 dni. Če tretji polnilni odmerek zamudite ali ga izpustite, je treba tofersen uporabiti čim prej, prvi vzdrževalni odmerek pa je treba dati čez 28 dni. Če vzdrževalni odmerek zamudite ali ga izpustite, je treba tofersen uporabiti čim prej. Naslednje vzdrževalne odmerke je treba nato dajati enkrat na vsakih 28 dni od zadnjega odmerka. Trajanje zdravljenja: Potrebo po nadaljevanju zdravljenja je treba redno preverjati in obravnavati individualno glede na bolnikovo klinično sliko in odziv na zdravljenje. • ***Starejši:*** Ni dokazov, da bi bilo treba odmerek tofersena prilagoditi. • ***Ledvična/jetrna okvara:*** Tofersena niso preučevali pri bolnikih z ledvično/jetrno okvaro. • ***Pediatrična populacija:*** Podatkov ni na voljo. • **Način uporabe:** Zdravilo je namenjeno za intratekalno uporabo z lumbalno punkcijo. Pred dajanjem tofersena je priporočljivo z iglo za lumbalno punkcijo odvzeti približno 10 ml likvorja. Tofersen se daje v obliki 1 do 3 minute trajajoče intratekalne bolusne injekcije z iglo za lumbalno punkcijo. • **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. • **Interakcije:** Sočasna uporaba drugih intratekalnih zdravil s tofersenom ni bila ocenjena in varnost teh kombinacij ni znana. Tofersen ni induktor ali zaviralec oksidativne presnove, ki jo posreduje CYP450, zato naj ne bi vplival na druga zdravila, ki medsebojno delujejo na te presnovne poti. • **Opozorila/previdnostni ukrepi:** • ***Postopek lumbalne punkcije:*** Pri lumbalni punkciji obstaja tveganje neželenih učinkov (npr. glavobol, bolečine v hrbtu, sindrom po lumbalni punkciji, okužba). •***Mielitis in/ali radikulitis; povečan intrakranialni tlak in/ali edem papile:*** Pri bolnikih, ki so se zdravili s tofersenom, so poročali o resnih primerih mielitisa in radikulitisa ter povečanega intrakranialnega tlaka in/ali edema papile. Če se pojavijo simptomi, ki ustrezajo tem neželenim učinkom, je treba začeti diagnostično oceno in zdravljenje v skladu s standardno oskrbo. •***Trombocitopenija in motnje koagulacije:*** Po subkutanem ali intravenskem dajanju protimiselnih oligonukleotidov so opazili trombocitopenijo in motnje koagulacije, vključno z akutno hudo trombocitopenijo. Če je klinično indicirano, je pred dajanjem tofersena priporočljivo opraviti laboratorijske preiskave trombocitov in koagulacije. • ***Ledvična toksičnost:*** Po subkutanem ali intravenskem dajanju protimiselnih oligonukleotidov so opazili ledvično toksičnost. Če je klinično indicirano, se priporoča testiranje beljakovin v urinu (po možnosti z vzorcem prvega jutranjega urina). Pri vztrajno zvišanih vrednostih beljakovin v urinu je treba razmisliti o nadaljnji oceni. • **Neželeni učinki:** • ***Zelo pogosti:*** povečano število levkocitov v likvorju, zvečane vrednosti beljakovin v likvorju, artralgija, mialgija, bolečina, utrujenost, zvišana telesna temperatura. • ***Pogosti:*** edem papile, nevralgija, aseptični meningitis, radikulitis, mielitis, mišično-skeletna togost. • **Poročanje o domnevnih neželenih učinkih:** Poročanje o domnevnih neželenih učinkih zdravila po izdaji dovoljenja za promet je pomembno. Omogoča namreč stalno spremljanje razmerja med koristmi in tveganji zdravila. Od zdravstvenih delavcev se zahteva, da poročajo o katerem koli domnevnem neželenem učinku zdravila na Javna agencija Republike Slovenije za zdravila in medicinske pripomočke, Sektor za farmakovigilanco, Nacionalni center za farmakovigilanco, Slovenčeva ulica 22, SI-1000 Ljubljana, Tel: +386 (0)8 2000 500, Faks: +386 (0)8 2000 510, e-pošta: h-farmakovigilanca@jazmp.si, spletna stran: www.jazmp.si. • **Imetnik dovoljenja za promet:** Biogen Netherlands B.V., Prins Mauritslaan 13, 1171 LP Badhoevedorp, Nizozemska • **Način izdajanja zdravila:** H. • **Opozorilo:** Pred predpisovanjem preberite celoten povzetek glavnih značilnosti zdravila. • **Datum priprave informacije:** 07/2024.

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INOVATIVNO ZDRAVLJENJE ZA VAŠE BOLNIKE z gMG, ki so POZITIVNI na AChR-Ab[1]

Prvi in edini Fc-fragment za zdravljenje gMG, ki je pokazal hitro, signifikantno in trajno izboljšanje sposobnosti opravljanja vsakodnevnih aktivnosti.[1-5]

Zdravilo Vyvgart je indicirano kot dodatek k standardni terapiji za zdravljenje odraslih bolnikov z generalizirano miastenijo gravis (gMG, generalised Myasthenia Gravis), ki so pozitivni na protitelesa proti acetilholinskim receptorjem (AChR, Acetylcholine Receptor).[1]

AChR-Ab, protitelo proti acetilholinskim receptorjem; **gMG,** splošna miastenija gravis; **Fc,** domena IgG

1. Povzetek glavnih značilnosti zdravila VYVGART. **2.** Zhu LN, *et al. Neural Regen Res*. 2023;18:1637-1644. **3.** Cavalcante P, *et al. Front Immunol*. 2024;15:1404191. **4.** Howard JF, *et al. Lancet Neurol*. 2021;20:526-536. **5.** Bril V, *et al.* Poster Presented at the (AAN) Annual Meeting; April 13-18, 2024; Denver, Colorado.

Skrajšan povzetek glavnih značilnosti zdravila VYVGART®

Skrajšan povzetek glavnih značilnosti zdravila. Pred predpisovanjem preberite celoten Povzetek glavnih značilnosti zdravila.

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8, kako poročati o neželenih učinkih.

Vyvgart 20 mg/ml koncentrat za raztopino za infundiranje (efgartigimod alfa)

Kakovostna in količinska sestava: Ena viala z 20 ml vsebuje 400 mg efgartigimoda alfa (20 mg/ml). Efgartigimod alfa je fragment Fc, pridobljen iz humanega rekombinantnega imunoglobulina G1(IgG1), proizvedenega v ovarijskih celicah kitajskega hrčka s tehnologijo rekombinantne DNK. **Terapevtske indikacije:** Zdravilo Vyvgart je indicirano kot dodatek k standardni terapiji za zdravljenje odraslih bolnikov z generalizirano miastenijo gravis (gMG, generalised Myasthenia Gravis), ki so pozitivni na protitelesa proti acetilholinskim receptorjem (AChR, Acetylcholine Receptor). **Odmerjanje in način uporabe:** Efgartigimod alfa mora dajati zdravstveni delavec pod nadzorom zdravnika z izkušnjami pri zdravljenju bolnikov z živčno-mišičnimi motnjami. Odmerjanje: Priporočeni odmerek je 10 mg/kg v obliki 1-urne intravenske infuzije, ki jo je treba dajati v ciklih infundiranja enkrat na teden 4 tedne. Nadaljnje cikle zdravljenja je treba aplicirati v skladu s klinično oceno. Pogostnost ciklov zdravljenja se lahko razlikuje glede na bolnika. V kliničnem razvojnem programu je bil najzgodnejši čas za začetek naslednjega cikla zdravljenja 7 tednov od začetnega infundiranja prejšnjega cikla. Pri bolnikih s telesno maso 120 kg ali več je priporočeni odmerek 1200 mg (3 viale) na infundiranje. *Izpuščeni odmerek:* Če načrtovano infundiranje ni možno, se lahko zdravljenje izvaja do 3 dni pred načrtovano časovno točko ali po njej. Nato je treba nadaljevati s prvotnim režimom odmerjanja, dokler se cikel zdravljenja ne konča. Če je treba odmerek odložiti za več kot 3 dni, odmerka ne smete dajati, da zagotovite dajanje dveh zaporednih odmerkov v presledku najmanj 3 dni. *Starejši:* Pri bolnikih, starih 65 let ali več, odmerka ni treba prilagajati. *Okvara ledvic:* Podatki o varnosti in učinkovitosti pri bolnikih z blago okvaro ledvic so omejeni; prilagajanje odmerka pri teh bolnikih ni potrebno. Podatki o varnosti in učinkovitosti pri bolnikih z zmerno ali hudo okvaro ledvic so zelo omejeni. *Okvara jeter:* Podatki za bolnike z okvaro jeter niso na voljo. Odmerka ni treba prilagajati. *Pediatrična populacija:* Podatkov ni na voljo. Način uporabe: Zdravilo se sme dajati samo z intravensko infuzijo. Zdravila ne dajajte kot intravensko potisno ali bolusno injekcijo. Pred uporabo ga je treba razredčiti z raztopino 9 mg/ml (0,9 %) natrijevega klorida za injiciranje. Zdravilo je treba dajati 1 uro. Pred dajanjem efgartigimoda alfa mora biti na voljo ustrezno zdravljenje infuzijskih reakcij in preobčutljivostnih reakcij. V primeru infuzijskih reakcij je treba infundirati počasneje, infundiranje prekiniti ali pa prenehati izvajati. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Sledljivost: Z namenom izboljšanja sledljivosti bioloških zdravil je treba jasno zabeležiti ime in številko serije uporabljenega zdravila. Bolniki z miastenijo gravis razreda V po merilih Ameriške fundacije za miastenijo gravis (MGFA): Zdravljenja z efgartigimodom alfa pri teh bolnikih niso proučevali. Upoštevati je treba zaporedje uvedbe zdravljenja med uveljavljenimi terapijami za MG-krizo in efgartigimodom alfa ter njihovo morebitno medsebojno delovanje. Okužbe: Ker efgartigimod alfa povzroči prehodno zmanjšanje ravni IgG, se lahko tveganje za okužbe poveča. Najpogostejše okužbe, opažene v kliničnih preskušanjih, so bile okužbe zgornjih dihal in okužbe sečil. Med zdravljenjem z zdravilom Vyvgart je treba bolnike spremljati glede kliničnih znakov in simptomov okužb. Pri bolnikih z aktivno okužbo je treba pretehtati razmerje med koristjo in tveganjem za ohranitev ali prekinitev zdravljenja z efgartigimodom alfa, dokler ni okužba odpravljena. Če se pojavijo resne okužbe, je treba razmisliti o odložitvi zdravljenja z efgartigimodom alfa, dokler ni okužba odpravljena. Infuzijske reakcije in preobčutljivostne reakcije: Pojavijo se lahko infuzijske reakcije, kot sta izpuščaj ali pruritus. V kliničnem preskušanju so bile infuzijske reakcije blage do zmerne in niso privedle do trajne prekinitve zdravljenja. Bolnike je treba med dajanjem zdravila in še 1 uro po njem spremljati glede kliničnih znakov in simptomov infuzijskih reakcij. Če pride do reakcije, je odvisno od resnosti reakcije treba infundirati počasneje, infundiranje prekiniti ali prenehati izvajati, in uvesti ustrezne podporne ukrepe. Ko reakcija izzveni, se lahko zdravljenje previdno nadaljuje odvisno od klinične ocene. V obdobju po začetku trženja so poročali o primerih anafilaktične reakcije. Ob sumu na anafilaktično reakcijo je treba dajanje zdravila Vyvgart takoj prekiniti in začeti ustrezno zdravljenje. Bolnike je treba obvestiti o znakih in simptomih preobčutljivostnih in anafilaktičnih reakcij ter jim svetovati, naj se v primeru pojava teh reakcij takoj obrnejo na svojega zdravstvenega delavca. Imunizacije: Vsa cepiva je treba uporabiti v skladu s smernicami za cepljenje. Varnost cepljenja z živimi ali živimi oslabljenimi cepivi in odziv na cepljenje s temi cepivi med zdravljenjem z efgartigimodom alfa nista znana. Pri bolnikih, ki se zdravijo z efgartigimodom alfa, cepljenje z živimi ali živimi oslabljenimi cepivi na splošno ni priporočljivo. Če je cepljenje z živimi ali živimi oslabljenimi cepivi potrebno, je treba ta cepiva uporabiti vsaj 4 tedne pred zdravljenjem in vsaj 2 tedna po zadnjem odmerku efgartigimoda alfa. Druga cepiva se lahko dajejo po potrebi kadar koli med zdravljenjem z efgartigimodom alfa. Imunogenost: Protitelesa proti efgartigimodu alfa niso imela opaznega vpliva na klinično učinkovitost ali varnost oziroma na farmakokinetične in farmakodinamične parametre. Imunosupresivi in antiholinesterazna zdravila: Pri zmanjšanju ali prekinitvi zdravljenja z nesteroidnimi imunosupresivi, kortikosteroidi in antiholinesteraznimi zdravili je treba bolnike skrbno spremljati glede znakov poslabšanja bolezni. Pomožne snovi z znanim učinkom: *Natrij:* To zdravilo vsebuje 67,2 mg natrija na viálo, kar ustreza 3,4 % največjega dnevnega vnosa 2 g natrija za odraslo osebo po priporočilih Svetovne zdravstvene organizacije (SZO). To zdravilo bo za dajanje nadalje pripravljeno z raztopino, ki vsebuje natrij, kar je treba upoštevati pri skupnem dnevnem vnosu natrija za bolnika iz vseh virov. *Polisorbati:* To zdravilo vsebuje 4,1 mg polisorbata 80 v vsaki viali, kar ustreza 0,2 mg/ml. Polisorbati lahko povzročijo alergijske reakcije. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Študij medsebojnega delovanja niso izvedli. Efgartigimod alfa lahko zmanjša koncentracije spojin, ki se vežejo na humani neonatalni receptor Fc (FcRn), tj. imunoglobulinov, monoklonskih protiteles ali derivatov protiteles. Če je mogoče, je priporočljivo, da se začetek zdravljenja s temi zdravili preloži na 2 tedna po zadnjem odmerku katerega koli cikla zdravljenja z zdravilom Vyvgart. Bolnike je treba skrbno spremljati glede predvidenega odziva na učinkovitost teh zdravil. Zamenjava plazme, imunoadsorpcija in plazmafereza lahko zmanjšajo ravni efgartigimoda alfa v obtoku. Vsa cepiva je treba uporabiti v skladu s smernicami za cepljenje. Pri bolnikih, ki se zdravijo z efgartigimodom alfa, cepljenje z živimi ali živimi oslabljenimi cepivi na splošno ni priporočljivo. Če je cepljenje z živimi ali živimi oslabljenimi cepivi potrebno, je treba ta cepiva uporabiti vsaj 4 tedne pred zdravljenjem in vsaj 2 tedna po zadnjem odmerku efgartigimoda alfa. **Plodnost, nosečnost in dojenje:** Nosečnost: Podatkov o uporabi efgartigimoda alfa pri nosečnicah ni. Znano je, da se protitelesa, vključno s terapevtskimi monoklonskimi protitelesi, aktivno prenašajo preko posteljice (po 30 tednih nosečnosti) z vezavo na FcRn. Efgartigimod alfa se lahko prenese z matere na razvijajoči se plod. Pričakuje se zmanjšanje pasivne zaščite novorojenca. Zato je treba razmisliti o tveganjih in koristih uporabe živih/živih oslabljenih cepiv pri dojenčkih, ki so bili *in utero* izpostavljeni efgartigimodu alfa. O zdravljenju nosečnic z zdravilom Vyvgart je treba razmisliti le, če klinične koristi odtehtajo tveganja. Dojenje: Ni podatkov o prisotnosti efgartigimoda alfa v materinem mleku, učinkih na dojenega otroka ali učinkih na proizvodnjo mleka. O zdravljenju žensk, ki dojijo, z efgartigimodom alfa je treba razmisliti le, če klinične koristi odtehtajo tveganja. Plodnost: Podatkov o vplivu efgartigimoda alfa na plodnost pri ljudeh ni na voljo. **Vpliv na sposobnost vožnje in upravljanja strojev:** Zdravilo Vyvgart nima vpliva ali ima zanemarljiv vpliv na sposobnost vožnje in upravljanja strojev. **Neželeni učinki:** Najpogosteje opaženi neželeni učinki so bile okužbe zgornjih dihal (10,7 %) in okužbe sečil (9,5 %). Pogosti (≥ 1/100 do < 1/10) neželeni učinki so bili še bronhitis, navzea, mialgija in proceduralni glavobol. V obdobju po začetku trženja so poročali o primerih anafilaktične reakcije. Pogostnost je neznana. Več informacij glede neželenih učinkov lahko najdete v Povzetku glavnih značilnosti zdravila. **Način in režim predpisovanja ter izdaje zdravila:** H - Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. **Imetnik dovoljenja za promet z zdravilom:** argenx BV, Industrieparkk-Zwijnaarde 7, 9052 Gent, Belgija **Številka dovoljenja za promet z zdravilom:** EU/1/22/1674/001 **Datum zadnje revizije besedila:** junij 2025

Poročanje o neželenih učinkih

Poročanje o domnevnih neželenih učinkih zdravila po izdaji dovoljenja za promet je pomembno. Omogoča namreč stalno spremljanje razmerja med koristmi in tveganji zdravila. Od zdravstvenih delavcev se zahteva, da poročajo o katerem koli domnevnem neželenem učinku zdravila na Javno agencijo RS za zdravila in medicinske pripomočke (h-farmakovigilanca@jazmp.si).

Samo za strokovno javnost.

SI-MG-2025-057-R2 I Datum priprave: avgust 2025

MEDISON | argenx

Evrysdi®
risdiplam

Zdravilo Evrysdi pri bolnikih s SMA ...

... spodbuja izražanje SMN beljakovin po celotnem telesu, vključno z osrednjim živčnim sistemom.[2]

... ohranja sposobnost požiranja in s tem tudi oralno prehranjevanje.[3]

... ima več kot 5-letne podatke o varnosti in učinkovitosti.[4]

... je edina neinvazivna SMA terapija, ki omogoča preprosto peroralno jemanje doma.[1]

Zdravilo Evrysdi je indicirano za zdravljenje 5q spinalne mišične atrofije (SMA) pri bolnikih s klinično diagnozo SMA tipa 1, tipa 2 ali tipa 3 ali z eno do štirimi kopijami SMN2.

1. Evrysdi® Povzetek glavnih značilnosti zdravila Evrysdi. Dostopano na: https://www.ema.europa.eu/sl/documents/product-information/evrysdi-epar-product-information_sl.pdf (dostopano 19.08.2025) 2. Messina S et al. J Clin Med. 2020;9(7):2222). | 3. Finkel RS et al International Annual Congress of the World Muscle Society 2023, Charleston, US. | 4. Mazurkiewicz-Bełdzińska M et al, Cure SMA Annual SMA Research & Clinical Care Meeting 2024, Austin, US. | 5. PBRER april 2025.

▼**Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Kako poročati o neželenih učinkih, si poglejte skrajšani povzetek glavnih značilnosti zdravila pod ‚Poročanje o domnevnih neželenih učinkih“.**
Ime zdravila: Evrysdi 0,75 mg/ml prašek za peroralno raztopino. **Kakovostna in količinska sestava:** Ena steklenička vsebuje 60 mg risdiplama v 2 g praška za peroralno raztopino. En mililiter pripravljene raztopine vsebuje 0,75 mg risdiplama. **Terapevtske indikacije:** Zdravilo Evrysdi je indicirano za zdravljenje 5q spinalne mišične atrofije (SMA) pri bolnikih s klinično diagnozo SMA tipa 1, tipa 2 ali tipa 3 ali z eno do štirimi kopijami *SMN2*. **Odmerjanje in način uporabe:** Priporočeni odmerek zdravila Evrysdi enkrat na dan je treba določiti glede na starost in telesno maso (glejte Povzetek glavnih značilnosti zdravila). Uporaba zdravila Evrysdi za zdravljenje SMA pri bolnikih, starih 2 meseca ali manj, je podprta s farmakokinetičnimi in varnostnimi podatki pri pediatričnih bolnikih, starih 16 dni in več. Peroralna uporaba. Zdravilo Evrysdi prašek za peroralno raztopino mora pred izdajo bolniku pripraviti zdravstveni delavec. Zdravilo Evrysdi je treba jemati enkrat na dan s hrano ali brez nje, vsak dan ob približno istem času; uporabiti ga je treba s priloženo peroralno brizgo za večkratno uporabo. Zdravila Evrysdi se ne sme mešati z mlekom ali mlečnimi formulami. Zdravilo Evrysdi je treba vzeti takoj potem, ko se ga izvleče v peroralno brizgo. Če se zdravilo Evrysdi polije ali pride na kožo, je treba predel umiti z milom in vodo. Po zaužitju zdravila Evrysdi mora bolnik popiti nekaj vode, da zagotovi, da je zdravilo v celoti pogoltnil. Če bolnik ne more požirati, je mogoče zdravilo Evrysdi prašek za peroralno raztopino dati po sondi/stomi. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** V študijah na živalih so opažali embrio-fetalno toksičnost. Bolnice in bolnike v obdobju plodnosti je treba seznaniti s temi tveganji. Uporabljati morajo visoko učinkovito kontracepcijo. Na podlagi opažanj v študijah na živalih bolniki ne smejo darovati semena. Učinkov zdravila Evrysdi na plodnost moških pri ljudeh niso raziskovali. Zdravilo Evrysdi vsebuje izomalt. Bolniki z redko dedno intoleranco za fruktozo ne smejo jemati tega zdravila. Zdravilo Evrysdi vsebuje 0,375 mg natrijevega benzoata na mililiter. Natrijev benzoat lahko poveča tveganje za zlatenico pri novorojenčkih. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Risdiplam se presnavlja predvsem z jetrnima encimoma flavin-monooksigenazo 1 in 3, pa tudi z encimi citokroma 450 1A1, 2J2, 3A4 in 3A7. Risdiplam ni substrat humane beljakovine MDR. Če se zdravilo Evrysdi uporabi sočasno z zaviralcem CYP3A, odmerka ni treba prilagoditi. Prilagoditev odmerka substratov CYP3A ni potrebna. Podatki *in vitro* kažejo, da lahko risdiplam v plazmi zviša koncentracijo zdravil, ki se odstranjujejo z MATE1 ali MATE2-K, npr. metformin. Če se sočasni uporabi ni mogoče izogniti, je treba bolnike nadzirati glede morebitnih toksičnih učinkov; če je treba, se lahko zmanjša odmerek sočasno uporabljenega zdravila. **Neželeni učinki**: Pri bolnikih, pri katerih se je SMA začela v obdobju dojenčka, so bili v kliničnih študijah najpogosteje opaženi neželeni učinki zvišana telesna temperatura, izpuščaj in driska. Pri bolnikih, pri katerih se je SMA začela pozneje, so bili v kliničnih študijah najpogosteje opaženi neželena učinki zvišana telesna temperatura, glavobol, driska in izpuščaj. Zgoraj navedeni neželeni učinki so se pojavili brez prepoznavnega kliničnega ali časovnega vzorca in so običajno kljub nadaljevanju zdravljenja minili tako pri bolnikih s SMA z začetkom v obdobju dojenčka kot s SMA s poznejšim začetkom. Poročanje o domnevnih neželenih učinkih: Poročanje o domnevnih neželenih učinkih zdravila po izdaji dovoljenja za promet je pomembno. Omogoča namreč stalno spremljanje razmerja med koristmi in tveganji zdravila. Od zdravstvenih delavcev se zahteva, da poročajo o katerem koli domnevnem neželenem učinku zdravila na: Javna agencija Republike Slovenije za zdravila in medicinske pripomočke, Sektor za farmakovigilanco, Nacionalni center za farmakovigilanco, Slovenčeva ulica 22, SI-1000 Ljubljana, Tel: +386 (0)8 2000 500, Faks: +386 (0)8 2000 510, e-pošta: h-farmakovigilanca@jazmp.si, spletna stran: www.jazmp.si. **Režim izdaje zdravila:** Rp/Spec **Imetnik dovoljenja za promet:** Roche Registration GmbH, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Nemčija. Za podrobnejše informacije glejte celoten Povzetek glavnih značilnosti zdravila.**Verzija: 2.0/25**

DODATNE INFORMACIJE SO NA VOLJO PRI: Roche farmacevtska družba d.o.o., Stegne 13G, 1000 Ljubljana
Datum priprave informacije: avgust 2025 M-SI-00001482(v1.0)

Samo za strokovno javnost

Roche

cutaquig®

Humani polispecifični imunoglobulin (SCIg) 165 mg/ml raztopina za injiciranje

Cutaquig® omogoča zdravljenje s subkutanimi polispecifičnimi imunoglobulini s samoinjiciranjem na domu, kar zmanjšuje pogostost obiskov bolnišnice[1-3]

Cutaquig® ima dobro dokazano učinkovitost in prenašanje ter omogoča pacientom, da prilagodijo zdravljenje na domu svojemu individualnemu življenjskemu slogu[2,3]

Cutaquig® zagotavlja priročno, individualizirano zdravljenje z različnimi velikostmi vial (1 g, 2 g, 4 g in 8 g) in shranjevanje pri sobni temperaturi (do 25 °C) do 9 mesecev[1]

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

IME ZDRAVILA Cutaquig® 165 mg/ml raztopina za injiciranje. **KAKOVOSTNA IN KOLIČINSKA SESTAVA:** Humani polispecifični imunoglobulin (s.c. Ig). 1 ml vsebuje: Humani polispecifični imunoglobulin 165 mg. Čistost vsaj 95% IgG. Največja vsebnost IgA je 300 mikrogramov/ml. **Terapevtske indikacije:** *Nadomestno zdravljenje odraslih ter otrok in mladostnikov (starih od 0 do 18 let)* pri sindromih primarne imunske pomanjkljivosti (PIP) z okvarjenim nastajanjem protiteles, sekundarnih imunskih pomanjkljivosti (SIP) pri bolnikih, ki trpijo zaradi hudih ali ponavljajočih se okužb, neučinkovitega protimikrobnega zdravljenja in bodisi dokazane odpovedi specifičnih protiteles (PSAF) ali serumske koncentracije IgG < 4 g/l. **Odmerjanje in način uporabe:** Nadomestno zdravljenje je treba uvesti in spremljati pod nadzorom zdravnika, izkušenega v zdravljenju imunskih pomanjkljivosti. Odmerek in shema odmerjanja sta odvisna od indikacije. Zdravilo je treba dajati po subkutani poti. Pri nadomestnem zdravljenju bo morda treba odmerek individualno prilagoditi posameznemu bolniku, odvisno od farmakokinetičnega in kliničnega odziva. Zdravilo Cutaquig® se lahko daje v rednih časovnih presledkih od vsakodnevnega odmerka do odmerka vsak drugi teden. Naslednje sheme odmerjanja so podane kot smernice. *Nadomestno zdravljenje pri sindromih primarne imunske pomanjkljivosti:* S shemo odmerjanja je treba doseči najnižjo koncentracijo IgG najmanj 5 do 6 g/l in jo vzdrževati znotraj mej referenčnega intervala serumskih IgG glede na starost. Morda bo znašal začetni odmerek vsaj 0,2 do 0,5 g/kg (1,2 do 3,0 ml/kg) telesne mase. Le-tega je morda treba razdeliti na več dni; najvišji dnevni odmerek znaša med 0,1 in 0,15 g/kg. Ko je doseženo stanje dinamičnega ravnovesja ravni IgG, se dajejo vzdrževalni odmerki v ponavljajočih se presledkih, da se doseže kumulativni mesečni odmerek od 0,4 do 0,8 g/kg (2,4 do 4,8 ml/kg) telesne mase. Vsak posamezni odmerek bo morda potrebno injicirati v različna mesta na telesu. *Nadomestno zdravljenje pri sekundarni imunski pomanjkljivosti:* Priporočeni odmerek, ki se daje v ponavljajočih se presledkih, da se doseže kumulativni mesečni odmerek od 0,2 do 0,4 g/kg (1,2 do 2,4 ml/kg) telesne mase. Hitrost infundiranja in količino zdravila, infundiranega v določeno mesto, prilagodimo glede na prenašanje posameznega bolnika. Priporočena začetna hitrost infundiranja je 15 ml/h/mesto. Od sedmega infundiranja naprej, lahko hitrost infundiranja počasi povišate na 25 ml/h/mesto. Priporočene hitrosti infundiranja na uro skupaj za vsa mesta: 30 ml/h za prvih 6 infundiranj, potem počasi zvišujemo na 50 ml/h in, v primeru, da bolnik to dobro prenaša, na 80 ml/h. Pri dojenčkih in otrocih se lahko mesto infundiranja menja na vsakih 5-15 ml. Pri odraslih se odmerke nad 30 ml lahko razdeli na željo bolnika. Število mest infundiranja ni omejeno. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. Zdravila Cutaquig® ne smete dajati intravensko. Prav tako zdravila ne smete dajati intramuskularno v primerih hude trombocitopenije in drugih motenj hemostaze. **Posebna opozorila in previdnostni ukrepi:** Priporočeno je, da ob vsakem dajanju zdravila Cutaquig® bolniku zabeležite ime in številko serije zdravila. To zdravilo vsebuje največ 90 mg maltoze na ml kot pomožne snovi. Moteča prisotnost maltoze v testih ravni glukoze v krvi lahko povzroči lažno povečane odčitke koncentracije in posledično neustrezno odmerjanje inzulina, kar lahko povzroči smrtno nevarno hipoglikemijo in smrt. Prav tako lahko primeri dejanske hipoglikemije ostanejo nezdravljeni. Če se zdravilo Cutaquig® po nesreči da v žilo, se lahko pri bolniku razvije šok. Priporočeno hitrost infundiranja, morate natančno upoštevati. Nekateri neželeni učinki se lahko pogosteje pojavijo pri bolnikih, ki prvič prejmejo humani polispecifični imunoglobulin, ali v redkih primerih, kadar se zdravilo s humanim polispecifičnim imunoglobulinom zamenja ali kadar je od zadnjega infundiranja minilo dalj časa. V primeru neželenih učinkov morate bodisi zmanjšati hitrost infundiranja ali infundiranje prekiniti. Potrebno zdravljenje je odvisno od vrste in resnosti neželenih učinkov. Če se razvije šok, je potrebno uvesti standardno medicinsko zdravljenje za šok. Prave alergijske reakcije so redke. Pojavijo se predvsem pri bolnikih s protitelesi proti IgA, ki jih je treba zdraviti posebej previdno. Pri bolnikih, ki imajo protitelesa proti IgA, pri katerih je zdravljenje s subkutanimi zdravili IgG edina možnost, je treba zdravljenje z zdravilom Cutaquig® strogo nadzorovati. Redko lahko humani polispecifični imunoglobulin sproži padec krvnega tlaka z anafilaktično reakcijo tudi pri bolnikih, ki so prenašali predhodno zdravljenje s humanim polispecifičnim imunoglobulinom. Z uporabo imunoglobulinov so povezani arterijski in venski trombembolični dogodki, vključno z miokardnim infarktom, možgansko kapjo, globoko vensko trombozo in pljučno embolijo. Pred uporabo imunoglobulinov morajo biti bolniki ustrezno hidrirani. Pri bolnikih z obstoječimi dejavniki tveganja za trombotične dogodke je potrebna previdnost. V povezavi s subkutanim zdravljenjem z imunoglobulini so poročali o pojavu sindroma aseptičnega meningitisa. Pri bolnikih, ki so prejemali zdravljenje z imunoglobulini, so poročali o hudih neželenih učinkih na ledvicah, zlasti pri uporabi zdravil, ki so vsebovala saharozo (zdravilo Cutaquig® ne vsebuje saharoze). Po injiciranju imunoglobulina lahko prehodno povečanje različnih pasivno prenesenih protiteles v bolnikovi krvi povzroči lažno pozitivne rezultate pri seroloških preiskavah. Pri dajanju zdravil, pripravljenih iz človeške krvi ali plazme, ni mogoče popolnoma izključiti prenosa povzročiteljev nalezljivih bolezni. To se nanaša tudi na doslej še neznane ali porajajoče se viruse in druge povzročitelje bolezni. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Uporaba imunoglobulinov lahko zmanjša učinkovitost cepiv z živimi oslabljenimi virusi, kot so cepiva proti ošpicam, rdečkam, mumpsu in noricam, za najmanj 6 tednov pa do 3 mesece. V primeru ošpic lahko opisano zmanjšanje učinkovitosti traja celo do enega leta. **Neželeni učinki** Občasno se lahko pojavijo neželeni učinki, kot so mrzlica, glavobol, omotica, povišana telesna temperatura, bruhanje, alergijske reakcije, navzea, artralgija, nizek krvni tlak in zmerna bolečina v križu. V redkih primerih lahko humani polispecifični imunoglobulini povzročijo nenadno zmanjšanje krvnega tlaka in v posameznih primerih anafilaktični šok, celo pri bolnikih, ki pri predhodnem zdravljenju niso pokazali znakov preobčutljivosti. Lokalne reakcije na mestih infundiranja so pogoste. **Posebna navodila za shranjevanje** Shranjujte v hladilniku. Ne zamrzujte. V času roka uporabnosti lahko zdravilo do 9 mesecev shranjujete pri sobni temperaturi (shranjujte pri temperaturi do 25 C) ne da bi ga v tem času ponovno hranili v hladilniku. **Način in režim izdaje:** H/Rp **Imetnik dovoljenja za promet z zdravilom:** Octapharma (IP) SPRL, Allée de la Recherche 65, 1070 Anderlecht, Belgija. Datum prve odobritve: 19. 8. 2019 **Datum zadnje revizije besedila:** 15.5.2024

Reference: 1.Povzetek glavnih značilnosti zdravila Cutaquig®. **2.** Kobayashi, R.H., et al., Clinical efficacy, safety and tolerability of a new subcutaneous immunoglobulin 16.5% [cutaquig®] in the treatment of patients with PID. Front Immunol, 2019. 10:40. **3.** Latysheva, E., et al., Efficacy and safety of cutaquig® in adults with PID: a prospective, open-label study. Immunotherapy, 2020. Epub, doi: 10.2217/ imt-2020-0012.

Samo za strokovno javnost. Pred predpisovanjem zdravila Cutaquig® si preberite zadnji veljavni Povzetek glavnih značilnosti zdravil. Datum priprave informacije: avgust 2025

octapharma

Zdravilo AMVUTTRA® (vutrisiran) omogoča HITER KNOCKDOWN* serumskega TTR v treh tednih po prvem odmerku*[1-4]

Zdravljenje z zdravilom AMVUTTRA® je povzročilo hiter knockdown serumskega TTR v treh tednih po prvem odmerku, z 88 % povprečnim znižanjem glede na izhodišče, ki se je ohranilo več kot 18 mesecev.[1,2]
* hitro znižanje ravni TTR

Indikacija
Zdravilo Amvuttra® je indicirano za zdravljenje dedne transtiretinske amiloidoze pri odraslih bolnikih s polinevropatijo 1. ali 2. stopnje (hATTR-PN) in za zdravljenje nemutirane ali dedne transtiretinske amiloidoze pri odraslih bolnikih s kardiomiopatijo (ATTR-CM).[2]

amvuttra (vutrisiran) 25 mg raztopina za injiciranje v napolnjeni injekcijski brizgi

hATTR = dedna transtiretinska amiloidoza; TTR, transtiretin
Reference: 1. Adams D, et al. Amyloid. 2023;30(1):18–26; **2.** AMVUTTRA® SmPC; **3.** Dasari AKR, et al. Biochemistry. 2022;61(21):2358–2365; **4.** Ghosh S, et al. Amyloid. 2023;30(4):379–393.

Skrajšan povzetek glavnih značilnosti zdravila

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.

Amvuttra 25 mg raztopina za injiciranje v napolnjeni injekcijski brizgi
Sestava zdravila: Ena napolnjena injekcijska brizga vsebuje natrijev vutrisiranat v količini, ki ustreza 25 mg vutrisirana, v 0,5 ml raztopine. **Terapevtske indikacije:** Za zdravljenje dedne transtiretinske amiloidoze pri odraslih bolnikih s polinevropatijo 1. ali 2. stopnje (hATTR-PN – hereditary transthyretin amyloidosis-polyneuropathy). Za zdravljenje nemutirane ali dedne transtiretinske amiloidoze pri odraslih bolnikih s kardiomiopatijo (ATTR-CM – transthyretin amyloidosis-cardiomyopathy). **Odmerjanje in način uporabe:** Zdravljenje je treba začeti čim prej v poteku bolezni, da se prepreči napredovanje invalidnosti. Odmerjanje Priporočeni odmerek zdravila Amvuttra je 25 mg v obliki subkutane injekcije enkrat na 3 mesece. Pri bolnikih, ki prejemajo zdravilo Amvuttra, se svetuje dodajanje vitamina A v odmerku približno 2500 i.e. do 3000 i.e. na dan. Odločitev o nadaljevanju zdravljenja pri bolnikih, pri katerih bolezen napreduje do polinevropatije 3. stopnje, je treba sprejeti po presoji zdravnika na podlagi splošne ocene koristi in tveganja. Podatkov o vutrisiranu pri bolnikih s srčnim popuščanjem razreda IV po merilih Newyoraškega združenja za srce (NYHA) in pri bolnikih, ki so hkrati v razredu III po NYHA ter v fazi bolezni III po merilih Nacionalnega centra za amiloidozo (NAC), je malo. Vendar ti podatki kažejo, da lahko bolniki, ki prejemajo vutrisiran, v primeru napredovanja v te stopnje ostanejo na zdravljenju. Posebne populacije *Starejši bolniki* Pri bolnikih, starih ≥ 65 let, prilagajanje odmerka ni potrebno. *Okvara jeter* Pri bolnikih z blago ali zmerno okvaro jeter prilagajanje odmerka ni potrebno. Vutrisirana niso preučili pri bolnikih s hudo okvaro jeter in ga ti bolniki smejo prejemati samo, če pričakovana klinična korist odtehta možno tveganje. *Okvara ledvic* Pri bolnikih z blago do zmerno okvaro ledvic prilagajanje odmerka ni potrebno. Vutrisirana niso preučili pri bolnikih s hudo ledvično okvaro ali končno odpovedjo ledvic in ga ti bolniki smejo prejemati le, če pričakovana klinična korist odtehta možno tveganje. *Pediatrična populacija* Varnost in učinkovitost zdravila Amvuttra pri otrocih ali mladostnikih, mlajših od 18 let, nista bili dokazani. Podatkov ni na voljo. Način uporabe Zdravilo Amvuttra je namenjeno samo za subkutano uporabo. Zdravilo Amvuttra lahko daje zdravstveni delavec, bolnik ali skrbnik. Bolniki ali skrbniki lahko injicirajo zdravilo Amvuttra po tem, ko jih je zdravstveni delavec poučil o pravilni tehniki subkutanega injiciranja. To zdravilo je pripravljeno za uporabo in je namenjeno samo za enkratno uporabo. Raztopino je treba vizualno pregledati glede delcev in obarvanja. Raztopine ne uporabite, če je obarvana ali so prisotni delci. Če je napolnjena injekcijska brizga shranjena na hladnem, je treba škatlo približno 30 minut pred dajanjem pustiti na sobni temperaturi, da se segreje. Subkutano injekcijo je treba injicirati v eno od naslednjih mest: trebuh, stegna ali nadlakti. Če se injicira v nadlaket, mora injekcijo dati zdravstveni delavec ali skrbnik. Zdravila se ne sme injicirati v brazgotinasto tkivo ali pordele, vnete ali otekle predele. Pri injiciranju v trebuh se je treba izogibati predelu okoli popka. **Kontraindikacije:** Huda preobčutljivost (npr. anafilaksa) na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Pomanjkanje vitamina A Zdravilo Amvuttra z zniževanjem ravni beljakovine transtiretina (TTR) v serumu povzroči znižanje ravni vitamina A (retinol) v serumu. Ravni vitamina A v serumu, ki so pod spodnjo mejo normalnih vrednosti, je treba korigirati in pred uvedbo zdravljenja z zdravilom Amvuttra oceniti kakršne koli očesne simptome ali znake zaradi pomanjkanja vitamina A. Bolniki, ki prejemajo zdravilo Amvuttra, morajo za zmanjšanje možnega tveganja očesnih simptomov zaradi pomanjkanja vitamina A peroralno jemati dodatek vitamina A v odmerku približno 2500 i.e. do 3000 i.e. na dan, vendar ne več. V prvih 60 dneh nosečnosti so lahko previsoke ali prenizke ravni vitamina A povezane s povečanim tveganjem za malformacije ploda. Zato je treba pred začetkom uporabe zdravila Amvuttra izključiti nosečnost, ženske v rodni dobi pa morajo uporabljati učinkovito kontracepcijo. Če ženska namerava zanositi, je treba dajanje zdravila Amvuttra in dodajanje vitamina A prekiniti ter nadzirati ravni vitamina A v serumu, ki se morajo vrniti na normalno raven, preden poskusi zanositi. V primeru nenačrtovane nosečnosti je treba zdravljenje z zdravilom Amvuttra prekiniti. Ni znano, ali dodajanje vitamina A med nosečnostjo zadošča za preprečevanje pomanjkanja vitamina A, če nosečnica nadaljuje s prejemanjem zdravila Amvuttra. Vendar pa zaradi mehanizma delovanja zdravila Amvuttra ni verjetno, da bi povečanje dodajanja vitamina A do več kot 3000 i.e. na dan med nosečnostjo popravilo ravni retinola v plazmi, je pa lahko škodljivo za mater in plod. Vsebnost natrija To zdravilo vsebuje manj kot 1 mmol (23 mg) natrija na ml, kar v bistvu pomeni 'brez natrija'. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Kliničnih študij medsebojnega delovanja niso izvedli. Ne pričakuje se, da bi vutrisiran povzročil medsebojno delovanje ali da bi nanj vplivali zaviralci ali induktorji encimov citokroma P450 ali da bi spremenil aktivnost prenašalcev. Zato se ne pričakuje, da bi imel vutrisiran klinično pomembne interakcije z drugimi zdravili. **Plodnost, nosečnost in dojenje:** Ženske v rodni dobi Zdravljenje z zdravilom Amvuttra znižuje ravni vitamina A v serumu. Previsoke ali prenizke ravni vitamina A so lahko povezane s povečanim tveganjem za malformacije ploda. Zato je treba pred uvedbo zdravljenja izključiti nosečnost, ženske v rodni dobi pa morajo uporabljati učinkovito kontracepcijo. Če ženska namerava zanositi, je treba zdravljenje z zdravilom Amvuttra in dodajanje vitamina A prekiniti ter nadzirati ravni vitamina A v serumu, ki se morajo vrniti na normalno raven, preden poskusi zanositi. Ravni vitamina A v serumu lahko ostanejo znižane še več kot 12 mesecev po zadnjem odmerku zdravila. Nosečnost Podatkov o uporabi zdravila Amvuttra pri nosečnicah ni. Zaradi možnosti tveganja za teratogenost, ki izhaja iz neuravnoteženih ravni vitamina A, zdravila Amvuttra ne smete uporabljati pri nosečnicah. Dojenje Ni znano, ali se vutrisiran izloča v materino mleko. Odločiti se je treba med prenehanjem dojenja in prenehanjem/prekinitvijo zdravljenja z zdravilom Amvuttra, pri čemer je treba pretehtati prednosti dojenja za otroka in prednosti zdravljenja za mater. Plodnost Podatkov o učinku zdravila Amvuttra na plodnost pri človeku ni. Študije na živalih niso pokazale vpliva na plodnost samcev ali samic. **Vpliv na sposobnost vožnje in upravljanja strojev:** Zdravilo Amvuttra nima vpliva ali ima zanemarljiv vpliv na sposobnost vožnje in upravljanja strojev. **Neželeni učinki:** Pogosti (≥ 1/100 do < 1/10): reakcije na mestu injiciranja, zvišane vrednosti alanin- aminotransferaze, zvišane vrednosti alkalne fosfataze v krvi. **Način/režim predpisovanja/izdaje zdravila:** Rp/Spec - Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet z zdravilom:** Alnylam Netherlands B.V., Antonio Vivaldistraat 150, 1083 HP Amsterdam, Nizozemska Številka(-e) dovoljenja za promet z zdravilom: EU/1/22/1681/001 **Datum zadnje revizije besedila:** 06/2025

Pred predpisovanjem se seznanite s celotnim Povzetkom glavnih značilnosti zdravila.

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Za več informacij nam pišite na: si-info@genesispharmagroup.com
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Datum priprave materiala: september 2025 AMV-SI-ADPN-09.2025

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