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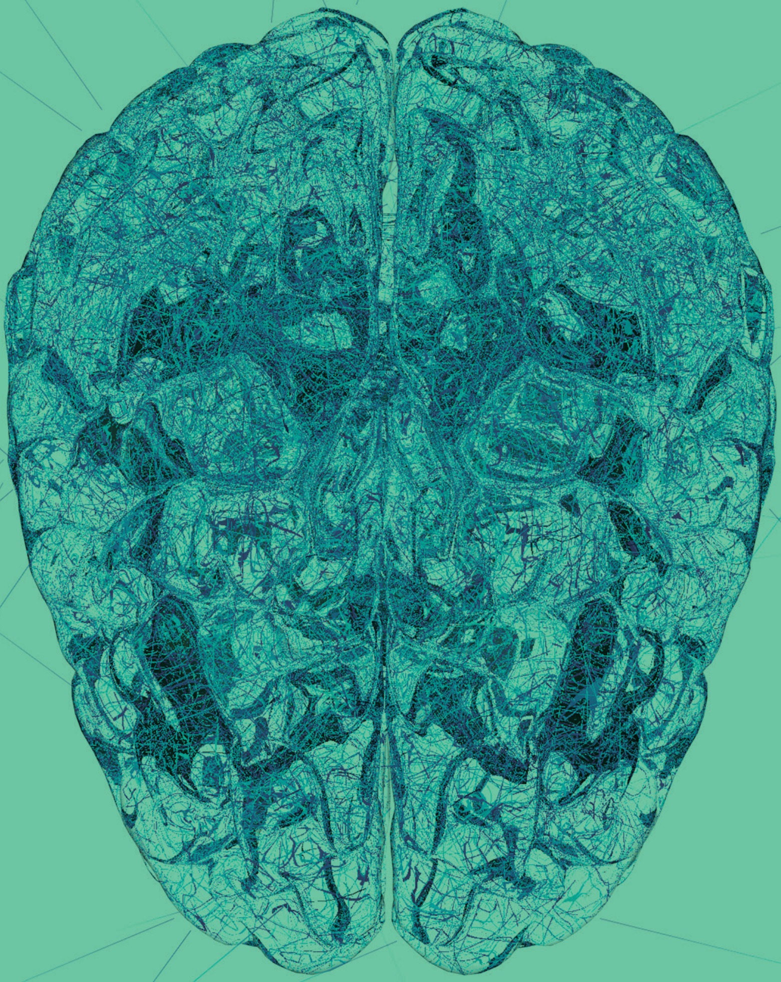
SLOVENIAN NEUROSCIENCE ASSOCIATION

SNC'17

SINAPSA NEUROSCIENCE CONFERENCE '17



29-30 September, 2017
LJUBLJANA, SLOVENIA

Univerza *v Ljubljani*
Medicinska fakulteta

Sinapsa Neuroscience Conference ‘17
Faculty of Medicine, Ljubljana, 29–30 September 2017

Organised by
SiNAPSA, Slovenian Neuroscience Association
Faculty of Medicine, University of Ljubljana

SNC’17 Programme Committee
Maja Bresjanac (Chair), Jure Bon, Hana Hawlina, David
Neubauer, Boštjan Rituper, Boris Rogelj

SNC’17 Organising Committee
Andraž Matkovič (Chair), Rok Berlot, Jure Bon, Maja Bresjanac
Mateja Drolec Novak, Blaž Koritnik, Dolores Trol

Conference was supported by
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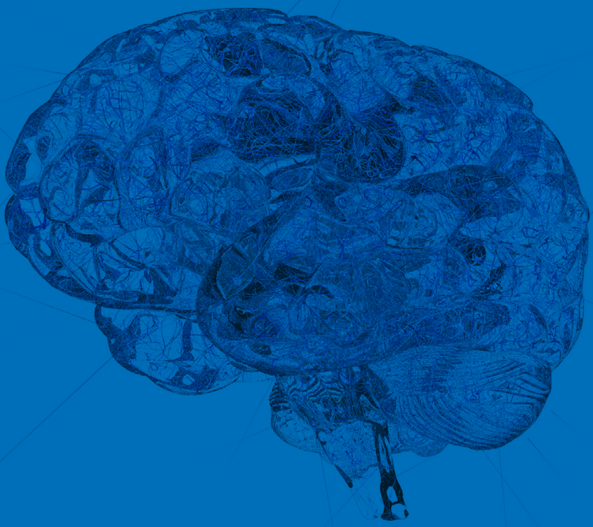

BOOK OF ABSTRACTS

www.sinapsa.org/SNC17
Faculty of Medicine, Ljubljana, Slovenia
29–30 September 2017

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Schedule at a glance

	Friday, 29 September		**Saturday,** 30 September		
08:00	**Registration** Poster exhibition area		**Registration** Poster exhibition area		08:00
09:00	**Opening of the SNC'17** | Hall II				09:00
10:00	Symposium **Deep brain stimulation: Application in adults and children with movement disorders** Hall II	Symposium **RNA binding proteins in neurodegenerative diseases** Hall III	Symposium **Long-term impact of early life exposures and stressors on the brain: Psychopathological dimensions of mental illnesses** Hall II	Symposium **Models, technologies and materials used in neuromodulation** Hall III	10:00
11:00					11:00
12:00	**Plenary talk** Andrew J. Lawrence Hall I		**Andrej O. Župančič Memorial lecture** Aletta Kraneveld Hall II		12:00
13:00	Poster session A	**Lunch**	Poster session B	**Coffee break & refreshments**	13:00
14:00	Symposium **Novel targets and strategies to treat neurodegenerative disease** Hall III	Educational workshop: neuroscience-based psychiatry **Session I** Hall II	Symposium **Glutamate and addiction: Vulnerability traits and treatment targets** Hall II	Symposium **Functional brain imaging in differential diagnosis of neurodegenerative brain disorders** Hall III	14:00
15:00					15:00
16:00	**Coffee break**		**Best poster award & closing of the SNC'17** | Hall II		16:00
17:00	Symposium **Plasticity of sensory motor network: from idea to the brain computer interface** Hall III	Educational workshop: neuroscience-based psychiatry **Session II** Hall II	**Coffee break** Neuroscience & society dialogue Hall II		17:00
18:00					18:00
19:00	Social evening Slamič Café				19:00
20:00					20:00
21:00					21:00

Satellite events

Krka sponsored symposium

Educational Workshop

	Friday, 29 September	
08:00	Registration Poster exhibition area	08:00
09:00	**Opening of the SNC'17** | Hall II	09:00
10:00	Satellite symposium **Krka sponsored closed event:** **Creating connections, coping with comorbidities** Hall I	10:00
11:00		11:00
12:00	**Plenary talk** Andrew J. Lawrence Hall I	12:00
13:00	Poster session A **Lunch**	13:00
14:00	Educational workshop: neuroscience-based psychiatry **Session I** Hall II	14:00
15:00		15:00
16:00	**Coffee break**	16:00
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21:00		21:00

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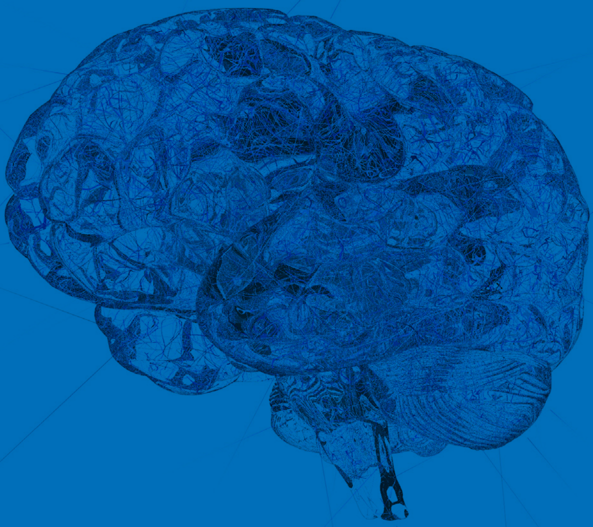

SiNAPSA Neuroscience Conference '17 Programme

www.sinapsa.org/SNC17
Faculty of Medicine, Ljubljana, Slovenia
29–30 September 2017

SiNAPSA Neuroscience Conference ’17 Programme

Friday, 29 September

8:00—19:00 **Registration** | Poster exhibition area

9:45—10:00 **Opening of the SNC’17** | Hall II

10:00—12:00 Symposium | Hall II. 27
Deep brain stimulation: Application in adults and children with movement disorders
Chairs: Maja Trošt, Norbert Kovacs

The prognosis for outcomes following DBS for children with Dystonia and other hyperkinetic movement disorders
Jean Pierre-Lin

How efficient is subthalamic deep brain stimulation in reducing dyskinesia in Parkinson’s disease?
Norbert Kovacs

The effect of subthalamic deep brain stimulation on non-motor symptoms in Parkinson’s disease
Maja Trošt

Targeting and clinical outcome of DBS in movement disorders patients
Mitja Benedičič

Personality changes after subthalamic deep brain stimulation in Parkinson’s disease
Dušan Flisar

Parkinsonian symptoms in patients with cervical dystonia treated with bilateral pallidal deep brain stimulation
Dejan Georgiev

10:00—12:00 Symposium | Hall III. 27
RNA binding proteins in neurodegenerative diseases
Chairs: Antonia Ratti, Francisco Baralle

New insights into the role of TDP 43 expression, structural feature and aggregation in disease pathogenesis
Francisco Baralle

TDP-43, stress granules and response to stress in ALS patients’ cells
Antonia Ratti

Drug screening in TDP-43 proteinopathies
Marco Baralle

Intranuclear RNA foci from C9ORF72 hexanucleotide expansion mutation form paraspeckle-like structures
Boris Rogelj

12:00—12:45 Plenary talk | Hall I. 25
Peptides and reward-seeking behaviour
Andrew J. Lawrence

13:00—14:30 **Poster session A** | Poster exhibition area
Cellular neuroscience A
Clinical neuroscience A
Cognitive neuroscience A
Molecular neuroscience A
Systems neuroscience

14:30—16:30 Symposium | Hall III. 32
Novel targets and strategies to treat neurodegenerative disease
Chair: Mojca Kržan

Multiscale simulation of monoamine oxidases: from chemical physics to neurodegeneration
Janez Mavri

No guts no glory: novel treatment strategy in Parkinson's disease
Aletta Kraneveld

Detection of dietary polyphenols and their metabolites
Sabina Passamonti

GABAergic system as a target for neuroprotection in AD model-rats
Baiba Jansone

16:30—17:00 **Coffee break**

17:00—19:00 Symposium | Hall III. 32
Plasticity of sensory motor network: from idea to the brain computer interface
Chair: Martin Rakuša

From the idea to the reaching – activity in sensory-motor network
Martin Rakuša

Stuttering: a model of impaired integration in sensory motor network
Pierpaolo Busan

Sensory motor network – brain computer interface
Piero Paolo Battaglini

Bimeo neuro-rehabilitation
Aleš Hribar

19:45—00:00 **SNC'17 Social event** | Slamič Café

Saturday, 30 September

8:00—17:00 **Registration** | Poster exhibition area

10:00—12:00 Symposium | Hall II 36
Long-term impact of early life exposures and stressors on the brain:
Psychopathological dimensions of mental illnesses
Chair: Gregor Majdič, Ana Počivavšek

Long lasting effects of prenatal, postnatal and pubertal stress in animal models
Ana Počivavšek

Permanent alteration of cortical/hippocampal glutamate and GABA neurotransmission
in adult rats following gestational cannabinoid exposure
Sarah Beggiato

Are offspring of mothers exposed to the ten-day war more vulnerable for mood disorders?
Liljana Šprah

Influence of prenatal exposure to testosterone on social behavior in Valproate mouse model of autism
Neža Grgurevič

10:00—12:00 Symposium | Hall III 36
Models, technologies and materials used in neuromodulation
Chair: Janez Rozman, Polona Pečlin

Surface electromyography and its potentials in assessment of neurodegenerative diseases and stroke rehabilitation
Aleš Holobar

A model and setup for opto-thermal stimulation of isolated porcine vagus nerve
Janez Rozman

Selective electrical stimulation and recording of an isolated porcine vagus nerve
Polona Pečlin

Materials and technologies used in crafting of multi-electrode spiral cuffs for VNS
Matjaž Godec

QMC-CT, a quantitative muscle assessment that patients understand and
that can get them to take-home full-body in-bed gym and FES
Ugo Carraro

Setup for experiments in focused pulsed ultrasound in translational biomedicine
Dejan Križaj

12:00—12:45 Andrej O. Županči Memorial lecture | Hall II 25
Digesting the gut-immune-brain axis in brain disorders
Aletta Kraneveld

13:00—14:30 **Poster session B** | Poster exhibition area
Cellular neuroscience B
Clinical neuroscience B
Cognitive neuroscience B
Molecular neuroscience B

14:30—16:30 Symposium | Hall II. 41
Glutamate and addiction: Vulnerability traits and treatment targets
Chair: Marco Leyton

Adolescent cocaine use perturbs glutamate synaptic maturation
Lucia Caffino

Glutamate signaling in serotonin transporter knockout rats prone to cocaine addiction
Judith Homberg

Mapping mGluR5 changes from initial drug exposure to addiction: PET [11C]ABP688 studies in humans
Marco Leyton

mGlu5 receptors and extinction of drug seeking
Andrew J Lawrence

14:30—16:30 Symposium | Hall III. 42
Functional brain imaging in differential diagnosis of neurodegenerative brain disorders
Chair: Maja Trošt, Daniela Perani

The PET perspective in early and differential diagnosis of dementia conditions
Daniela Perani

In vivo cholinergic basal forebrain atrophy predicts future cognitive decline in de novo PD
Chesney Craig

Structural network alterations and cognitive decline in Parkinson’s disease
Rok Berlot

Automated differential diagnosis of parkinsonian syndromes using FDG-PET image analysis
Tomaž Rus

Different FDG-PET metabolic patterns in parkinsonian syndromes
Maja Trošt

16:30—17:00 **Best poster award & closing of the SNC’17** | Hall II

17:00—17:30 **Coffee break**

17:30—19:00 **Neuroscience & Society Dialogue** | Hall II

Poster sessions

Friday, 29 September

13:00—14:30 **Cellular neuroscience A** 47

CEL.01 **RNA foci, transcribed from C9ORF72 expansion, form intranuclear paraspeckle-like bodies**
Ana Bajc Česnik

CEL.03 **Lateral fluid percussion injury induces astrocytosis and microgliosis without a neuronal loss in the rat frontal cortex**
Petra Dolenec

CEL.05 **The mechanism of folding and trafficking of the human dopamine transporter (hDAT) and its mutants associated with infantyle parkinsonism-dystonia**
Hafiz Muhammad Mazhar Asjad

CEL.07 **Innervation of primary human skeletal muscle cells induces isoform-specific upregulation of Na+/K+-ATPase subunits**
Vid Jan

13:00—14:30 **Clinical neuroscience A** 50

CLI.01 **Connective tissue dysplasia in young person: psychophysiological assessments and manual dexterity**
A. Gataullina

CLI.03 **Crossed cerebellar diaschisis detected with BOLD MRI cerebrovascular reactivity**
Martina Sebök

CLI.05 **Influence of transcutaneous electrical stimulation of the spinal cord on vegetative regulation of cardiac activity**
Guzel Fanisovna Khafizova

13:00—14:30 **Cognitive neuroscience A** 53

COG.01 **The peculiarities of brain activation during delayed visual recognition: fMRI-study**
Anastasia K. Neklyudova

COG.03 **Regulation of brain activity with neurofeedback in ADHD children**
Joanna Jarmolowska

COG.05 **Acute effects of dominant or submissive body pose adoption on thermosensitivity and pain threshold**
Dušanka Novaković

COG.07 **The influence of emotional stimuli on P3 in an »oddball« paradigm**
Nastja Tomat

COG.09 **Comprehensive understanding of instrumental description of psychophysically elicited somatosensory (pain) perceptions**
Kaja Meh

13:00—14:30 **Molecular neuroscience A** 59

MOL.05 **Localization of dipeptide repeat proteins and their interaction with lipid droplets in model cell lines**
Anja Pucer Janež

MOL.11 **Protein aggregation of TRIOBP-1 in patients with schizophrenia**
Nicholas J. Bradshaw

MOL.13 **TNIK gene and its alternative splicing regulation during neuronal differentiation**
Valentina Gumina

MOL.15 **Proteins binding to (C4G2)n RNA repeats**
Mirjana Malnar

MOL.17 **I-motifs and protonated hairpins forming on the anti-sense DNA d(GGCCCC)n expansions in C9ORF72**
Anja Kovanda

13:00—14:30 **Neuroscience methods A**. 57

MET.01 **Supraspinal influence on modulation of motor evoked potentials in the leg muscles during transcutaneous electrical stimulation of the human spinal cord**
L. M. Bikchentaeva

MET.03 **Stability and reliability of resting heart rate variability in healthy young adults**
Breda Podjaveršek

13:00—14:30 **Systems neuroscience** 64

SYS.01 **Influence of hypogravitation on the functional state of the myoneural synapses of rat soleus muscle**
I. D. Lvova

Saturday, 30 September

13:00—14:30 **Cellular neuroscience B** 49

CEL.02 **Role of astrocytes in survival of carbon monoxide-intoxicated neuronal cells, treated with hyperbaric oxygen**
Klara Bulc-Rozman

CEL.04 **TDP-43 expression in the parietal cortex and the hippocampus following a single traumatic brain injury in the mouse**
Petra Dolenec

CEL.06 **An approach to study cholesterol-rich domains in the outer leaflet of the plasma membrane of pituitary lactotrophs**
Boštjan Rituper

13:00—14:30 **Clinical neuroscience B** 52

CLI.02 **recoveriX – Brain-computer interface controlled avatar and functional electrical stimulation: clinical study for motor function rehabilitation after stroke**
Nensi Murovec

CLI.04 **Vascular physiology of CO_2: impact on cerebrovascular reactivity and neurovascular coupling**
C.H.B. van Niftrik

13:00—14:30 **Cognitive neuroscience B** 55

COG.04 **Why accountants compromise on their fiduciary duties: fMRI evidence on the role of the human mirror neuron system**
Mina Ličen

COG.06 **Neural coding mechanisms underlying spatial working memory**
Nina Purg

COG.08 **Transdisciplinary approach to comprehensive explanation of psychically modulated sensory (pain) information**
Dejan Georgiev

COG.10 **Nature of memory engrams: conserved wiring and computational logic of cell assemblies**
Grace E. Fox

13:00—14:30 **Molecular neuroscience B** 61

MOL.02 **17β-estradiol differentially modulates ecto-5’-nucleotidase activity in the hippocampal synaptosomes of male and female rats in vitro**
Natasa Mitrovic

MOL.06 **Phosphorylation of FUS impairs its nucleocytoplasmic shuttling**
Helena Motaln

MOL.10 **Solving structures of ALS associated proteins**
Vera Župunski

MOL.12 **Ibuprofen increased bilirubin neurotoxicity by interacting with albumin-bilirubin complex**
Ane-Mary Arčan

MOL.14 **Post-ischemic administration of erythropoietin: effects on the brain damage in rats exposed to focal cerebral ischemia**
Jasenka Mršić-Pelčić

MOL.16 **Comparison of small RNA expression in muscle tissue of patients with amyotrophic lateral sclerosis and healthy age-matched controls**
Anja Kovanda

13:00—14:30 **Neuroscience methods B** 58

MET.02 **The effects of muscle trapezius latent trigger point vibration on postural stability**
S. Sabitova

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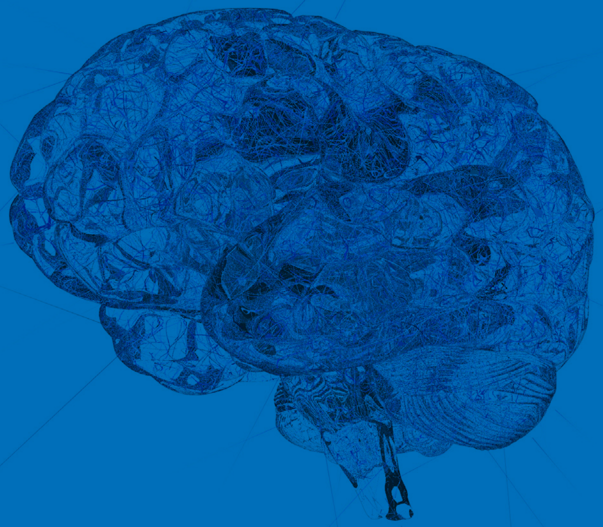

Educational workshop on neuroscience-based psychiatry

www.sinapsa.org/SNC17/workshop
Faculty of Medicine, Ljubljana, Slovenia
29 September 2017

Friday, 29 September

14:30—16:30 **Educational workshop on neuroscience-based psychiatry** | Hall II 75
Session I

Borderline personality disorder
Bojana Avguštin Avčin

Psychotic disorders
Borut Škodlar

16:30—17:00 **Coffee break**

17:00—19:00 **Educational workshop on neuroscience-based psychiatry** | Hall II 75
Session II

Addiction
Mirjana Radovanović

Psychosomatic disorders
Maja Rus Makovec

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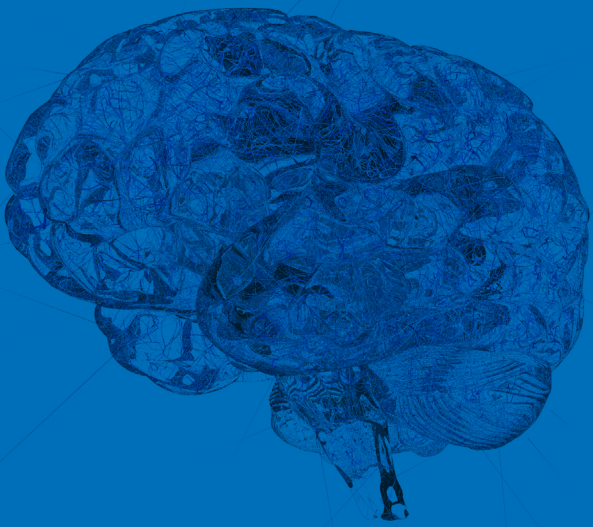

Krka sponsored symposium

Creating connections, coping with comorbidities

www.sinapsa.org/SNC17/krka-symposium
Faculty of Medicine, Ljubljana, Slovenia
29–30 September 2017

Friday, 29 September

10:00—12:00 Krka sponsored symposium | Hall I
Creating connections, coping with comorbidities

Prof. Blanka Kores-Plesničar, MD, PhD
University Psychiatric Hospital, Ljubljana, Slovenia

Assoc. Prof. Peter Pregelj, MD, PhD
University Psychiatric Hospital, Ljubljana, Slovenia

Sławomir Murawiec, MD, PhD
Dialog– Teraphy Center, Warsaw, Poland

Bogdan Rusu, MD
Pucioasa City Hospital, Dâmbovița County, Romania

12:00—12:45 Plenary talk | Hall I. 25
Peptides and reward-seeking behaviour
Andrew J. Lawrence

13:00—14:30 **Lunch**

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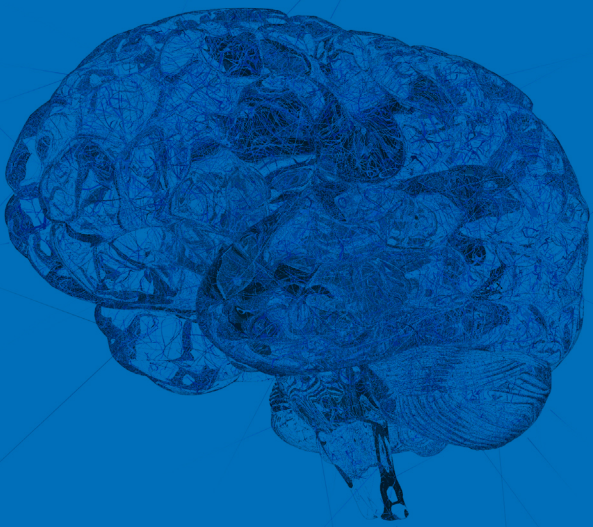

General information

www.sinapsa.org/SNC17
Faculty of Medicine, Ljubljana, Slovenia
29–30 September 2017

General Information

Venue
Faculty of Medicine, Univesity of Ljubljana
Korytkova 2, SI-1000 Ljubljana, Slovenia

Contact E-mail
For general queries, please write to: snc17@sinapsa.org

Registration and Information Desk
For further information about registration, please contact the Registration Office:
Tel.: +386 1 2417 136
Fax: +386 1 2417 296
e-mail: registration@cd-cc.si

The Registration Desk will be located in the foyer of Faculty of Medicine and open as follows:
Friday, 29 September, 8:00–19:00
Saturday, 30 September, 8:00–17:00

Information for Poster Presenters
There are no strict requirements regarding poster size. The poster boards allow posters up to 120 cm tall and 90 cm wide.
Presenters are advised to mount their posters on Friday morning and leave them up until the closing of the SNC'17.
The presenters are requested to be present and available for questions and discussion at the specified time-slot:
A - Friday 13:00-14:30; B - Saturday 13:00-14:30.

Information for Speakers
For oral presentations a computer projection system will be provided in the lecture hall. To ensure smooth and timely progression of the sessions, presentations should be submitted in advance of the relevant symposium.
Presenters can either send the presentation by e-mail to snc17@sinapsa.org, or submit it on a suitable electronic medium (CD, USB drive) either at the time of registration or on the day of the symposium, but no later than 15 minutes before the start of the session. Presenters should name the presentation file by their last name. Using the computer available in the lecture hall is a preferred method of presentation. If a presenter plans to use his/her own laptop, they should notify the organizers in advance of the session. Advance requests are required also for slide or video projection.

Internet
Wireless internet will be avaliable at the conference venue.

Conference Identification Badge
A conference identification badge will be included in the conference material provided upon registration. There will be no admittance to the Scientific Sessions without the conference badge.

Attendance Certificate
A Certificate of Attendance will be issued to all registered participants.

CME Certificate
Members of the Slovenian Medical Chamber will receive CME (Continuing Medical Education) credits.

Coffee Breaks
During breaks, refreshments will be available free of charge to participants wearing congress badges.

Social Programme

SNC’17

Saturday, 29 September, 20:00 - 00:00

Join us at the Slamič Café (Kersnikova ulica 1, http://www.slamic.si/) for a relaxing evening with drinks, music and dancing.

The social evening officialy starts at 9pm but you are welcome to join us from 8pm onwards.

Committees and Organisation

SiNAPSA Neuroscience Conference ‘17 was organised by
SiNAPSA, Slovenian Neuroscience Association
Faculty of Medicine, University of Ljubljana

SNC’17 Programme Committee
Maja Bresjanac (Chair)
Jure Bon
Hana Hawlina
David Neubauer
Boštjan Rituper
Boris Rogelj

SNC’17 Organising Committee
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Jure Bon
Maja Bresjanac
Mateja Drolec Novak
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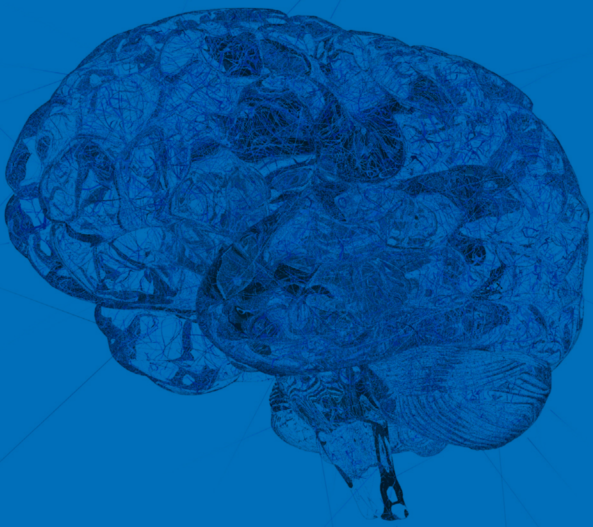

Abstracts

SNC'17 Plenary and Special Lectures

www.sinapsa.org/SNC17
Faculty of Medicine, Ljubljana, Slovenia
29–30 September 2017

Friday, September 29th, 12:00

Peptides and reward-seeking behaviour

Andrew J. Lawrence

Florey Institute of Neuroscience & Mental Health, University of Melbourne, Victoria, Australia

Relapse and hazardous drinking represent the most difficult clinical problems in treating patients with alcohol use disorders. Stress is a key precipitant of relapse, and relaxin-3 signaling modulates both stress responses and alcohol intake. We, therefore, examined a role for the relaxin-3 system in alcohol-seeking. In iP rats, icv microinjection of a selective RXFP3 antagonist prevented the yohimbine-induced reinstatement of alcohol-seeking, discrete microinjections implicated the dorsal BNST and central amygdala as loci. Relaxin-3 neurons are predominantly located in the pontine nucleus incertus (NI) which is highly sensitive to CRF. Intra-NI microinjection of a selective CRF1 receptor antagonist (CP376395) attenuated yohimbine-induced reinstatement of alcohol-seeking. After long-term voluntary alcohol intake in iP rats, qPCR revealed upregulation of mRNA encoding CRF1 and RXFP3 receptors in NI. We also found CRF within the NI, which was confirmed in rat and CRF-Cre x TdTomato reporter mouse brain. These data suggest NI neurons contribute to reinstatement of alcohol seeking, via an involvement of CRF1 signaling. The NI also receives orexinergic innervation and so we undertook analogous experiments. Bilateral NI injections of the OX2 receptor antagonist TCS-OX2-29 attenuated yohimbine-induced reinstatement of alcohol seeking, while the OX1 receptor antagonist SB-334867 had no effect. Orexin-A depolarized NI neurons recorded in coronal brain slices, sensitive to bath application of TCS-OX2-29, but not SB-334867. These data suggest an excitatory orexinergic input to NI contributes to yohimbine-induced reinstatement of alcohol seeking, predominantly via local OX2 receptor signaling. Collectively, these data implicate CRF and orexin inputs to relaxin-3 neurons of the NI in alcohol-seeking.

Saturday, September 30th, 12:00

Digesting the gut-immune-brain axis in brain disorders

Aletta Kraneveld

Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science and Institute for Risk Assessment Sciences, Faculty of Veterinary Medicine, Utrecht University, The Netherlands

Many CNS disorders are associated with gastrointestinal deficits characterized by motility problems, constipation or diarrhea, (low-grade) inflammation, abdominal pain and discomfort. The frequently reported leaky gut, intestinal inflammation and changes in the composition of the microbiome in patients point to the relevance of gut-microbiome-immune-brain axis in neurodevelopmental and neurodegenerative disorders such as autism spectrum disorder and Parkinson’s disease. Based on (pre)clinical data the talk will shed some light on the possible mechanism of the crosstalk between gut and brain in CNS disorders with a focus on immunological mechanisms. The first part of the talk will present (pre)clinical data on gut-immune-brain axis in autism spectrum disorders focusing on the role of the microbiome, immune system (food allergy) and mechanistic target of rapamycin (mTOR). In the second part, the relevance of gut-brain axis in Parkinson’s disease will be presented. Clinical data from patients show a leaky gut, changed microbiome composition, enhanced markers of microbial translocation and higher levels of relevant inflammatory profiles associated with an increased expression of the pattern recognition receptor, Toll like receptor 4 (TLR4) in the colon. TLR4 plays a fundamental role in pathogen recognition and activation of the innate immune system. Both human and animal studies suggest that TLR4-mediated gut-induced neuroinflammation could play an important role in intestinal as well as central neurodegenerative processes in Parkinson’s disease.

A poor gut function leads to a poor brain function; therefore targeting the microbiome and mucosal immune system with medical food interventions and/or pharmaceutical compounds could be a new approach for the therapy of CNS disorders.

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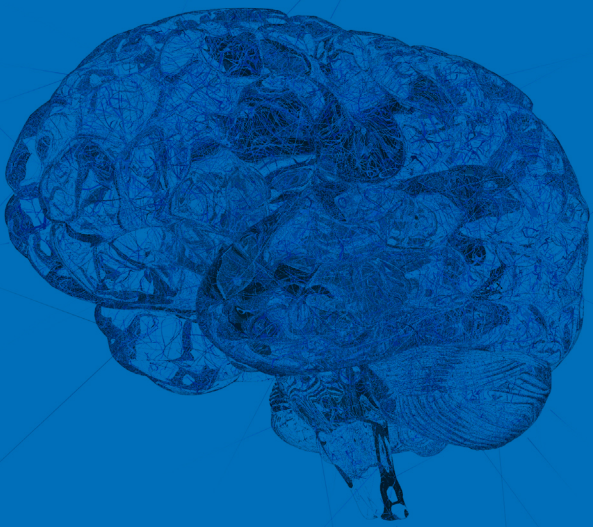

Abstracts

SNC'17 Thematic Symposia

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Faculty of Medicine, Ljubljana, Slovenia
29–30 September 2017

Friday, September 29th, 10:00 [Symposium: Deep brain stimulation: Application in adults and children with movement disorders]

The prognosis for outcomes following DBS for children with Dystonia and other hyperkinetic movement disorders

Jean Pierre-Lin

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This talk will focus on the demographics of hyperkinetic movement disorders, outcome measures and how to understand the impact of DBS in childhood hyperkinetic movement disorders.

Friday, September 29th, 10:00 [Symposium: RNA binding proteins in neurodegenerative diseases]

New insights into the role of TDP 43 expression, structural feature and aggregation in disease pathogenesis

Francisco Baralle

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ALS and FTLD are characterized by neuronal inclusions of TDP-43. It is also well established that significant variations of TDP-43 levels in the cell are deleterious. TDP-43 autoregulates its cellular levels by binding to its own pre mRNA and inducing its nuclear degradation by an NMD independent mechanism.

We have also developed a cellular model of aggregation based only on the specific TDP-43 amino acid sequences necessary to trigger aggregate formation and trapping of endogenous TDP-43 into a non-functional insoluble form. This shows that the aggregates result in TDP 43 loss of function.

Our recent data shows that the structural determinants of TDP-43 sequestering by aggregates are not only specific amino acid sequences such as the C-terminal prion-like Q/N domain but also conformational features of its N-terminal domain. We have shown that both in cell culture and in transgenic Drosophila strains the presence of aggregates leads to TDP-43/TBPH loss of function and their elimination result in an increase of functional TDP-43 as measured by splicing changes in endogenous genes. The transgenic fly exhibits also a phenotype with reduced lifespan, early locomotion defects, and neuromuscular junction abnormalities. Although the aggregate inducer is expressed constitutively the fly does not present an early onset of the locomotion phenotype. In this regard, we have observed that a physiological, age-related and evolutionary conserved 3–4 fold drop of TDP-43/TBPH levels in the brain happens in mice and Drosophila. In the latter organism, in the constitutive presence of aggregates, the onset of the locomotion phenotype coincides with the maximum reduction of TDP-43/TBPH levels during aging. A similar process may be acting in humans determining the usual late onset of ALS/FTD.

Keywords: TDP43, structure, aggregation

Friday, September 29th, 10:00 [Symposium: Deep brain stimulation: Application in adults and children with movement disorders]

How efficient is subthalamic deep brain stimulation in reducing dyskinesia in Parkinson's disease?

Norbert Kovacs

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Background: Dyskinesia is among the most troublesome symptoms of advanced Parkinson's disease (PD). The recently developed Unified Dyskinesia Rating Scale (UDysRS) can measure simultaneously several subjective and objective aspects of dyskinesia irrespective of the other motor symptoms of PD. Despite the advantages of deep brain stimulation (DBS), previous studies on DBS have not used the UDysRS yet.

Methods: In this prospective study, 71 consecutive patients undergoing DBS implantation were enrolled. Patients were examined twice: 1 week prior to the DBS implantation (baseline) and 12 months postoperatively. The severity of PD-related symptoms was assessed by the Movement Disorders Society Unified PD Rating Scale (MDS-UPDRS). Presence and severity of dyskinesia were specifically measured by the UDysRS and patient diaries.

Results: At baseline, all 71 patients had dyskinesia, but 1 year after DBS implantation, 25 patients were dyskinesia-free, and an additional 19 had only mild dyskinesia. The total score on the UDysRS decreased from 38.0 ± 17.8 to 10.8 ± 13.0 (p &lt; 0.001). Besides this, all parts of the UDysRS showed significant improvement after STN DBS treatment, and the magnitude of these changes had a large effect size. The total score of MDS-UPDRS improved from 76.5 ± 24.3 to 60.4 ± 21.4 points (p &lt; 0.001).

Conclusions: Based on our results, STN DBS can efficiently improve dyskinesia in advanced Parkinson's disease.

Keywords: deep brain stimulation, Parkinson's disease, dyskinesia

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Friday, September 29th, 10:00 [Symposium: RNA binding proteins in neurodegenerative diseases]

TDP-43, stress granules and response to stress in ALS patients' cells

Claudia Colombrita (1), Valentina Gumina (1,2), Annamaria Maraschi (1), Alberto Doretti (1,2), Cinzia Tiloca (1), Vincenzo Silani (1,2), Antonia Ratti (1,2)

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Abnormal cytoplasmic aggregates of TDP-43 protein represent a neuropathological hallmark of both familial and sporadic ALS and FTD diseases. TDP-43 is a mainly nuclear RNA-binding protein with multiple roles in RNA metabolism, including splicing, miRNA biogenesis, but also mRNA stability and transport. Our laboratory first demonstrated that in response to environmental insults TDP-43 is recruited into the cytoplasm within stress granules (SG), dynamic protein/RNA complexes which temporarily form to block translation. It has been recently suggested that in a condition of prolonged stress, as it occurs in the neurodegenerative process, SG would progressively fail to disassemble due to impaired autophagic/lysosomal activities and would turn into pathological TDP-43–containing inclusions. However, whether conditions of chronic stress induce the formation of SG has never been proven since they have been shown to form only upon short, sub-lethal stress exposure in vitro. We investigated this hypothesis by reproducing a status of chronic stress in primary fibroblasts and iPSC-derived motoneurons which were exposed to low doses of sodium arsenite for a prolonged timeframe. Formation of SG was observed in healthy control and ALS patients cells with differences in SG dynamics and protein components compared to acute stress SG. In mutant TARDBP and C9ORF72 cells, we also observed differences in SG number and size in a gene-specific manner. Our findings support the hypothesis that SG may represent the prelude to TDP-43 pathological aggregates in a condition of chronic and prolonged insult and may contribute to triggering neurodegeneration in ALS.

Keywords: stress granules, ALS, neurodegeneration, RNA-binding protein

Friday, September 29th, 10:00 [Symposium: Deep brain stimulation: Application in adults and children with movement disorders]

The effect of subthalamic deep brain stimulation on non-motor symptoms in Parkinson’s disease

Maruša Mencinger, Tamara Remšak, Sanja Šešok, Aleš Pražnikar, Dušan Flisar, Dejan Georgiev, Mitja Benedičič, Maja Trošt

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Aim: Surgical treatment of advanced Parkinson’s Disease (aPD) in one of the continuous treatments that significantly improve patient’s and caregiver’s quality of life. Although it is a standard treatment, a long term follow-up results are scarce. We are presenting the results of the observational follow-up study of 19 consecutive aPD patients who underwent STN DBS surgery.

Methods: At baseline (few days before surgery) patients underwent the following assessments of motor and non-motor symptoms: MDS-UPDRS III (ON phase), MMSE, MOCA, BDI, HAS, SCOPA-PC, NMSS, PDSS-2, PDQ39, PD NMSS and Stark-Apathy. The same evaluation was performed 6 months, 1 year, 2 and 3 years after surgery. Paired student T-test was performed to compare the baseline with the follow-up evaluations. A subgroup of 12 patients underwent comprehensive neuropsychological assessment which provided basic measures of psychomotor speed, attention span, memory processing of verbal and visual material and visuospatial ability (RBANS), verbal fluency task, attentional (Stroop) and executive task (TOL). Mood was evaluated by a self-rating questionnaire (CAD).

Results: The average age of aPD patients at baseline was 57.5 ± 7.0 years, 13 were male, average PD duration was 13.9 ± 4,6 years, their MMSE was 26.7 ± 1.6 and MoCA 25.9 ± 3.0. The results of this follow-up study show that most patients experienced a lessening of non-motor symptoms of the disease and an improvement in general well-being. Additionally, our findings implicate stability of attention, memory processing, verbal fluency and executive functions during the first year after STN DBS, which is in the line with some previous studies.

Conclusion: STN DBS treatment has a stable beneficial effect on non-motor symptoms in PD.

Keywords: Parkinson’s disease, subthalamic deep brain stimulation, non-motor symptoms

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Friday, September 29th, 10:00 [Symposium: Deep brain stimulation: Application in adults and children with movement disorders]

Targeting and clinical outcome of DBS in movement disorders patients

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Aim: A systematical analysis of the location of the deep brain electrodes inside the subthalamic nucleus was performed in order to improve the preoperative imaging protocol for targeting and to assess the surgical accuracy

Methods: Coordinates of the planned target point according to the anterior and posterior commissural points are determined using preoperative MRI scanning protocols for STN nucleus and are usually modified intraoperatively according to micro-electrode recording and clinical examination. Postoperative CT scans performed day after STN electrode implantation were merged on a planning station and compared to the preoperative targeting plan. Placement accuracy of the electrodes was assessed on the basis of lateral and antero-posterior errors.

Results and conclusion: Preliminary results show that the accuracy of our protocol is similar to data obtained from previously published studies. Continuous audit of the process is necessary in order to improve preoperative imaging protocols and placement accuracy, which correlates to the clinical outcome of DBS in movement disorder patients.

Friday, September 29th, 10:00 [Symposium: RNA binding proteins in neurodegenerative diseases]

Drug screening in TDP-43 proteinopathies

Marco Baralle

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ALS is a neurodegenerative disease characterized by loss of motor neuron activity. Finding an ALS effective therapy depends on the understanding of its pathogenic mechanisms and in the availability of models that reproduce the pathological hallmarks of the disease seen in the tissues of human patients. TDP-43 inclusions are the main histologic feature of ALS. However, the exact pathogenic role of these aggregates is still under debate. Regardless of the role played by the inclusions, their reduction represents an important therapeutic pathway. In fact, removal of the potential intrinsic toxicity or more likely the elimination of self-templating conformers that can sequester TDP-43 in aggregates leading to a depletion of its soluble functional form may prove beneficial for the patient. This type of approach has been difficult up to now because of the lack of a good model of TDP-43 aggregation.

We have created a HEK293 cell line that stably expresses one single copy of the transgene EGFP-TDPF4L-12XQ/N construct. The transgene, which is biologically inactive for TDP-43 function due to the mutations in the RNA-binding domains, aggregates and sequesters endogenous TDP-43 with concomitant loss of its function on splicing regulation.

As a proof of principle for its eventual use in high throughput screening, we identified a series of compounds that were able to clear the aggregates and restore TDP-43 dependent splicing activity. Analysis of the pathway being used by the cell in the enhanced aggregate clearance showed it was occurring via the proteosomal pathway, independently of autophagy.

Finally, this cell line is being used to test an in-house library of small molecules to search for compounds that induce aggregate clearance. Several compounds showed clearance activity in a dose-dependent manner without affecting the other cell physiology parameters and restored TDP-43 functionality. The data of these studies up to now will be presented.

Keywords: TDP-43, ALS, drug screen

Friday, September 29th, 10:00 [Symposium: Deep brain stimulation: Application in dults and children with movement disorders]

Personality changes after subthalamic deep brain stimulation in Parkinson’s disease

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Deep brain stimulation (DBS) is a routine therapeutic procedure for the treatment of various medication resistant neurological and psychiatric disorders. Besides its numerous benefits, various psychiatric side effects have been described. In Parkinson’s disease (PD) patients treated with subthalamic nucleus (STN) DBS apathy, hallucinations, compulsive gambling, hyper sexuality, cognitive difficulties and depression were observed. Most of them were only temporary and manageable after resetting of the stimulation parameters.

Certain research also points to patients’ personality changes after the beginning of DBS treatment, but research in this area is still insufficient and the results are varied. Should personality changes really occur, they should be specifically defined (i.e. irritability, lack of initiative, lack of perseverance etc.)

The aim of our study was to determine the effect of STN DBS on patient’s personality. We studied 25 PD patients who have been treated with STN DBS for at least half a year (mean duration 34.1 ± 22.9 months). Possible postoperative personality changes were evaluated using: the Iowa Scales of Personality Change (Barrash, 1997) which are completed by the caregiver, the Big Five Inventory (John, Donahue and Kentle, 1991) and the Psychological Well-Being Scales (Ryff, 1989).

It is of great importance to recognize possible postoperative personality changes to offer an adequate psychological assistance to patients and their caregivers.

Keywords: deep brain stimulation, personality changes

Friday, September 29th, 10:00 [Symposium: RNA binding proteins in neurodegenerative diseases]

Intranuclear RNA foci from C9ORF72 hexanucleotide expansion mutation form paraspeckle-like structures

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The expansion mutation of the GGGGCC repeat in the gene C9ORF72 is the most common genetic cause of FTLD and ALS. It is transcribed both from the sense and the antisense strands leading to the formation of nuclear RNA foci, which may sequester specific RNA binding proteins and affect various steps of post-transcriptional gene regulation. Core paraspeckle proteins SFPQ, NONO and PSPC1 bind to (G4C2)n repeat RNA in vitro, and colocalize with nuclear RNA foci in transfected cells and brain tissue of C9ORF72 mutant carriers at post-mortem. Sense RNA foci lead to an increased number of SFPQ-stained subnuclear bodies, which form independently of the known paraspeckle platform long non-coding RNA NEAT1. Furthermore, (G4C2)72 RNA foci also colocalized with paraspeckle-associated associated Alu repeat-containing RNAs, indicating that (G4C2)n RNA foci might replace NEAT1 as a scaffold of paraspeckle-like structures. Our results suggest that (G4C2)n RNA foci form paraspeckle-like structures, which function in similar fashion as paraspeckles and modulate nuclear compartmentalization of paraspeckle-bound RNAs.
Keywords: amyotrophic lateral sclerosis, frontotemporal dementia, C9orf72, RNA foci, paraspeckles

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Friday, September 29th, 10:00 [Symposium: Deep brain stimulation: Application in dults and children with movement disorders]

Parkinsonian symptoms in patients with cervical dystonia treated with bilateral pallidal deep brain stimulation

Dejan Georgiev

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Background: GPi-DBS is an established treatment option in patients with medically refractory dystonia. Few studies have reported the appearance of distinct parkinsonian signs with chronic GPi stimulation in these patients, such as gait disturbances or micrographia. However, there is no study evaluating post-GPi-DBS parkinsonian signs with a universal assessment tool, nor have any of the studies included a control group of dystonia patients on conventional treatments.

Methods: Twenty-four cervical dystonia patients treated with bilateral GPi-DBS (14 females; mean age 63.8 ± 7.8 y; 2 in combination with minor facial, and 1 in combination with minor trunk involvement) and 22 age, gender, handedness and disease duration matched unoperated patients with cervical dystonia (17 females; mean age 60.2 ± 10.2), were recruited. All patients underwent a standardized neurological examination including the BFMDRS for evaluation of dystonic symptoms and the MDS-UPDRS part III for assessing presence and severity of parkinsonian signs.

Results: There was a significant improvement of dystonia in the DBS group pre vs. post operation (BFMDRS 12.0 ± 2.4 vs. 6.8 ± 1.1, p = .038). BFMDRS of unoperated patients was 5.4 ± 1.9. GPi-DBS patients had higher MDS- UPDRS-III scores compared to the non-surgical patients (15.9 ± 6.7 vs. 6.4 ± 5.1, p &lt; .001). Patients on stimulation had higher subscores in all bradykinesia items compared to unoperated dystonia patients (all Bonferroni corrected, p &lt; .001). In addition, the limb rigidity score was higher in operated patients, p = .046. However, there was no difference between groups in the subscores for the speech, the overall tremor subscore, the ability to rise from a chair, gait, freezing of gait, or postural stability.

Conclusions: GPi-DBS dystonia patients had significantly higher MDS-UPDRS scores than unoperated patients. This was mostly due to higher scores on bradykinesia items, whereas gait, speech or postural stability subscores were not significantly different between groups. Further studies are needed to elucidate the mechanisms of this GPi-DBS-induced parkinsonian symptom in dystonia patients.
Keywords: GPi deep brain stimulation, cervical dystonia, Parkinsonian symptoms, bradykinesia

Friday, September 29th, 14:30 [Symposium: Novel targets and strategies to treat neurodegenerative disease]

Multiscale simulation of monoamine oxidases: from chemical physics to neurodegeneration

Janez Mavri

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Monoamine oxidase (MAO), which exists in two isozymic forms, MAO A and MAO B, is an important flavoenzyme responsible for the metabolism of biogenic amines such as dopamine, serotonin and norepinephrine. In this work, we present atomic details of the rate-limiting step of dopamine degradation by MAO B, which consists of the hydride transfer from the methylene group of the substrate to the flavin moiety of the enzyme. This contribution builds on our previous quantum chemical study of the same reaction using a cluster model (1), but now considering the full dimensionality of the hydrated enzyme. Well converged activation free energies were calculated by employing the empirical valence bond (EVB) approach of Warshel and coworkers (2). We show that the MAO B enzyme is specifically tuned to catalyze the hydride transfer step from the substrate to the FAD prosthetic group and that it lowers the activation barrier by 12.1 kcal/mol compared to the same reaction in aqueous solution, a rate enhancement of more than 8 orders of magnitude (3). The calculated barrier in the enzyme of 16.1 kcal/mol is in excellent agreement with the experimental value of 16.5 kcal/mol. Path integral calculation of H/D kinetic isotope effect for MAO B will be discussed (4). Results for simulation of MAO A catalyzed decomposition of noradrenaline will be given (5) and the effects of MAO A point mutations on decomposition of phenylethylamine will be presented (6). The relevance of MAO inhibition for prevention of neurodegeneration will be discussed (7). Experimental and computational results for H/D isotope effect for binding affinity of ligands to histamine receptor H2 will be presented (8).

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Friday, September 29th, 17:00 [Symposium: Plasticity of sensory motor network: from idea to the brain computer interface]

From the idea to the reaching – activity in sensory-motor network

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Background: Actual reaching requires the contribution of several cortical areas, which are connected in the frontoparietal network. Imaginary movements activate similar cortical and subcortical areas to actual movements, mainly in the frontoparietal network. The aim of our work was to further explore cortical activity during reaching preparation and separate ideational from action part of motor programming.

Methods: Twenty-one right-handed healthy volunteers performed actual and imagined reaching. EEG and EMG were recorded. EEG was averaged on target onset. Event related (de)synchronization (ERD/ERS) and Low-Resolution Brain Electromagnetic Tomography (sLORETA) were analyzed.

Results: Actual reaching started approximately 360 ms after target onset. Pre-target and pre-movement ERD were found in actual and imagined movements as well as ERS rebounds after reaching finished.

Cortical activity, evaluated with sLORETA, during actual reaching was always stronger than during imagined reaching with three key differences. The first difference was from 160 ms to 220 ms after visual target presentation in the frontal and parietal regions. The second difference was evident from 220 ms to 320 ms in the premotor cortex. The third difference was evident from 320 ms to the reaching onset, mainly in the perirolandic region.

Conclusion: Our results demonstrated wide activation of frontoparietal network during actual and imagined reaching preparation with specific changes in upper alpha and beta frequency bands. Ideational and ideomotor processes could differently activate similar cortical networks, where the former preferably activates visual-related and the latter motor-related regions of the frontoparietal network.

Keywords: reaching, event related potential, event related desynchronisation, low resolution brain electromagnetic tomography

Friday, September 29th, 14:30 [Symposium: Novel targets and strategies to treat neurodegenerative disease]

No guts no glory: novel treatment strategy in Parkinson’s disease

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Parkinson’s disease (PD) clinical picture is usually dominated by motor impairment. However, non-motor symptoms, such as cognitive decline and gastrointestinal dysfunctions, may already develop before the motor symptoms and are major determinants of quality of life. The dopamine precursor levodopa is the most commonly used drug in the treatment of motor symptoms but has serious side-effects and does not stop the degeneration process. Moreover, gastrointestinal dysfunctions of PD patients interfere with the absorption of levodopa and modify the effectiveness of the drug. There is a great need for additional therapies that reduce/modulate both motor and non-motor symptoms. We have shown that a diet containing nutritional precursors and cofactors required for membrane phospholipid synthesis, as well as prebiotic fibers, had therapeutic effects in a mouse model for PD. The effects of combined administration of the dietary intervention together with levodopa treatment are also studied in this murine PD model. C57BL/6J mice were injected with rotenone or vehicle in the striatum. The diet intervention started four weeks after surgery when PD-like symptoms were developed. The effects of oral treatment with different doses of levodopa were assessed weekly. Motor and cognitive functions were tested, intestinal transit and colon length were analyzed and histological examination of the brain and the colon was assessed. Our results show that rotenone-induced motor and non-motor problems were alleviated by the therapeutic dietary intervention. Levodopa showed an additive beneficial effect on motor performance in rotenone-treated animals fed with the diet. No negative interaction effects were found between the diet and levodopa treatment. Our results suggest that the dietary intervention might confer clinical benefits on patients receiving levodopa treatment.

Keywords: dietary intervention, mice, rotenone

Friday, September 29th, 17:00 [Symposium: Plasticity of sensory motor network: from idea to the brain computer interface]

Stuttering: a model of impaired integration in sensory motor network

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Developmental stuttering (DS) is a disturbance in the rhythm of speech, where people are not able to utter words in a fluent manner. It is common in childhood but it can persist into adulthood, with consequences on quality of life. DS is a neural disturbance that affects the motor system: it is characterized by abnormal speech/motor brain cortical activity, as well as by impairments in white matter integrity, especially in motor networks. Moreover, it is characterized by impairments in cortico-striato-thalamo-cortical networks. This pattern of impaired activity allows considering stuttering, and especially persistent stuttering in adulthood, as a model of abnormal sensorimotor integration. Here, I will try to describe our recent research findings in this field, obtained by using tools such as transcranial magnetic stimulation (TMS), electroencephalography (EEG), TMS/EEG co-registration and magnetoencephalography (MEG). Briefly, we will be able to support the vision that suggests DS as a general motor disturbance in which the excitatory/inhibitory ratio of (intra)cortical motor circuits and the muscular interplay are altered, thanks to a series of TMS studies conducted to investigate excitability of corticospinal and corticobulbar pathways, registering from hand/tongue muscles, also during motor tasks not directly related to speech. This vision is supported by the evidence that the motor cortex is able to activate different networks in DS and fluent speakers from a temporal/spatial point of view (TMS/EEG co-registration). Finally, EEG/MEG data will be able to define as the stuttering brain is characterized by a different modulation of (especially) motor rhythms, useful to fulfill motor programs.

Keywords: developmental stuttering, motor system, transcranial magnetic stimulation, electroencephalography, TMS/EEG co-registration

Friday, September 29th, 14:30 [Symposium: Novel targets and strategies to treat neurodegenerative disease]

Detection of dietary polyphenols and their metabolites

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We have been interested in checking whether dietary polyphenols can be transported from the blood into the brain, under normal conditions. Our investigation was meant at providing data in support to the observation that moderate, life-long consumption of wine protected against a cognitive decline in advanced age (1). These effects seemed to be related to the non-alcoholic fraction of wine (2), while ethanol is regarded as a cause of cognitive decline (3). A recent intervention study showed that grape extracts administered for 6 months could prevent metabolic changes in some brain cortex areas in subjects with a mild decline in cognition (4). Other animal experiments showed that grape extracts protected rats from neurodegenerative changes (5,6).

To further advance our understanding of these observations, it is essential to establish if dietary polyphenols circulating in the blood can cross the blood-brain barrier and attain predictably effective concentrations in the brain, so to modulate cellular or molecular functions. Anthocyanins are flavonoid pigments abundantly occurring in red berries and wine. They are limitedly absorbed from the digestive tract, attaining very low concentrations in the blood (0.1–1 μM). At these concentrations, they are bioactive, triggering arterial relaxation and cardioprotection. Do they pass the blood-brain barrier? To address this question, we decided to inject in the vein a small amount of cyanidin 3-glucoside (C3G; the most abundant dietary anthocyanin) and measure it into the brain and other organs of the rat, for a pharmacokinetic study. Our data point to an apparent equilibrium of C3G between the blood and the brain (7).

Even more interesting is the finding that the blood-brain barrier allows the selective passage of some metabolites of dietary polyphenols that are formed in the colon by the gut microbiota (8). These data show that the brain is the target of dietary polyphenols and their metabolites, which are to be numbered as chemical entities linking the gut, and the environment, to the brain.

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Friday, September 29th, 17:00 [Symposium: Plasticity of sensory motor network: from idea to the brain computer interface]

Sensory motor network – brain computer interface

Piero Paolo Battaglini

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Sensory motor networks are a plastic organization of the central nervous system that accounts for the quality of its performance. Based on connections, they can modify and improve themselves with training and also recover from damage, depending on the kind and extension of the injury. One way to obtaining this result without a massive physical training is to use neurofeedback (NF) or its operational side, brain computer interfaces (BCI). NF is used to train the brain to produce the proper rhythms that, for any reason, have been lost or deteriorated. In this case, the electroencephalography (EEG) of the subject is recorded, abnormal rhythms, or their relationships, are detected and the subject is somehow rewarded for producing the correct ones. In our lab, this has been shown to improve cognitive parameters in Parkinson patients and to be effective in children with Attention Deficit and Hyperactivity Disorder (ADHD) syndrome. BCI are systems that, excluding the physiological output pathways (nerves and muscles), allow to drive external devices using brain signals only. As to motor rehabilitation, many of the adopted procedures are based on the assumption that spatial and frequency distribution of the activity of local neuronal population mimics the spatial and frequency distribution of activity during motor imagery (MI). This allows the development of methods which are based on recovery of mental representation of action (MI) and use its EEG correlate so as to facilitate patients in re-learning to control movements of their body. An example of this approach will be given regarding Parkinson patients.

Keywords: neurofeedback, brain-computer interface, Parkinson, ADHD

Friday, September 29th, 17:00 [Symposium: Plasticity of sensory motor network: from idea to the brain computer interface]

Bimeo neuro-rehabilitation

Aleš Hribar, Matjaž Mihelj

Kinestica d.o.o., Ljubljana, Slovenia and Faculty of Electrical Engineering, University of Ljubljana, Slovenia

Bimeo is a sensor based upper extremity rehabilitation system. It makes therapy motivating and rewarding for patients and facilitating for therapists. The patient is encouraged to use the more affected arm, supported by the activity of the less affected arm. The Bimeo merges virtual reality gaming with proven rehabilitation methods. The therapy is focused on the activity of daily living type exercises, cognitive tasks and specific tasks for objective motor function assessment. A clinician can monitor patient’s progress and personalize the therapy program according to patient’s needs. Rehabilitation process becomes more effective and consecutively shorter.

Patients are engaged in a motivating rehabilitation environment. Therapy modes are set up in seconds using quickly interchangeable therapy attachments. Intuitive software and wireless sensing units empower therapists with a hassle free operation.

Keywords: neuro-rehabilitation, stroke, patients, medical device

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Friday, September 29th, 14:30 [Symposium: Novel targets and strategies to treat neurodegenerative disease]

GABAergic system as a target for neuroprotection in AD model-rats

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Important hallmarks of Alzheimer’s disease (AD) are neuroinflammation, disbalanced neurotransmission and the loss of synaptic plasticity, that impair neural circuitries and result in cognitive deficits in AD. Since the 1970/80s, the deficiency of cholinergic and glutamatergic processes have been considered as most essential in AD, whereas GABAergic neurotransmission has been generally thought to be well preserved. Recently, however, GABAergic system has been found to act as a substrate for synaptic plasticity, suggesting its compensatory role in the cognitive deficits observed early in AD (Nava-Mesa et al., 2014). Moreover, the accumulating evidence suggests that GABAergic activities are closely related to immune processes, and thus the GABAergic neurotransmitter system might represent an important therapeutic target in modulating neuroinflammatory processes. Our data demonstrate that GABA-A and GABA-B agonists muscimol and baclofen at very low doses (0.01–0.05 mg/kg ip) are able to protect against spatial memory/learning impairments and neuroinflammation, as well as regulate expression of acetylcholinesterase and GABA-production enzyme glutamate decarboxylase in brain regions of a non-transgenic rodent model (streptozocin icv) of AD. Multifactorial therapies that combine modulation of different neurotransmission systems, including the GABAergic system, emerge as a crucial tool for the future treatment strategies of AD.

Keywords: STZ, muscimol, baclofen, learning, memory

Saturday, September 30th, 10:00 [Symposium: Long-term impact of early life exposures and stressors on the brain: Psychopathological dimensions of mental illnesses]

Long lasting effects of prenatal, postnatal and pubertal stress in animal models

Gregor Majdič

Institute of Preclinical Sciences, Veterinary Faculty, University of Ljubljana, Slovenia and Institute of Physiology, Medical Faculty, University of Maribor, Slovenia

Stress is a physiological response of an organism to the immediate danger that helps to ensure the survival of the individual. However, many studies in recent years have shown that prolonged exposure to stress hormones, mainly glucocorticoids secreted from adrenal glands, could have deleterious effects on the function of different organs, in particularly brain. Prolonged exposure to stress in humans is connected with depressive and anxiety disorders, and some studies suggest that stress during vulnerable developmental periods could permanently affect brain development and consequently its function in the adult life. The brain is sensitive to stress hormones during different developmental periods both prenatally and after birth, and some recent studies, including ours, have shown that pubertal period is yet another period of brain sensitivity to stress hormones. In our studies we are exploring long lasting effects of stress during this vulnerable period of brain development in laboratory mice, using different stress paradigms such as prenatal stress caused to pregnant mice by injections, postnatal maternal separation stress or social isolation during puberty. Our results demonstrate that brain is sensitive to different stressors at all periods studied with different effects for the behavior of adult mice. Prenatal stress in mothers causes long lasting effects on aggressive behavior in male offspring of stressed mothers, while pubertal social isolation affects social behavior in adult mice, and these behavioral effects are seen even after resocialization, suggesting that social isolation during puberty causes long lasting effects on brain function.

Keywords: mouse, brain, stress, adult behavior, gene expression

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Saturday, September 30th, 10:00 [Symposium: Models, technologies and materials used in neuromodulation]

Surface electromyography and its potentials in assessment of neurodegenerative diseases and stroke rehabilitation

Aleš Holobar

Faculty of Electrical Engineering and Computer Science, University of Maribor, Slovenia

Noninvasive surface electromyography has demonstrated a remarkable progress in the last decade. It can no longer be perceived as a source of highly interferential signals, but rather as a realm of highly precise information about the final outputs of the central nervous system, also during long-term and dynamic muscle contractions. Advanced computer-aided techniques have been proposed for identification and assessment of individual motor unit and motor neuron activities out of surface electromyograms, in both healthy and pathological conditions. In this talk, we will illuminate the advantages of surface electromyography and its latest contributions to the understanding and assessment of pathophysiology of neurodegenerative diseases, such as essential and Parkinsonian tremor. We will further demonstrate the efficiency of surface electromyography in direct neural code estimation and discuss its applications in advanced rehabilitation of stroke patients.

Keywords: surface electromyography, motor units, neural codes, neurodegenerative diseases, stroke rehabilitation

Saturday, September 30th, 10:00 [Symposium: Long-term impact of early life exposures and stressors on the brain: Psychopathological dimensions of mental illnesses]

Elevated kynurenine pathway metabolism during neurodevelopment: Implications for brain and behavior

Ana Počivavšek

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Distinct abnormalities in tryptophan metabolism via the kynurenine pathway have been reported in schizophrenia (SZ), a catastrophic neurodevelopmental psychiatric disorder. Kynurenic acid (KYNA), an endogenous antagonist of α7 nicotinic acetylcholine (α7nACh) and NMDA receptors, is increased in the brain of patients with SZ. Based on the neurodevelopmental hypothesis of SZ etiology, we have developed a model to study the KYNA hypothesis of SZ (Pocivavsek et al., Psychopharmacology, 2014). The bioprecursor to KYNA, kynurenine (100 mg/day), is fed to pregnant Wistar dams from embryonic day 15 to 22 (control: ECon; kynurenine-treated: EKyn). Tissue KYNA levels remain increased in the hippocampus of adult EKyn animals and prenatal kynurenine treatment results in significant cognitive dysfunctions in adulthood. As disturbances in sleep can often aggravate illness severity for SZ patients and plausible hypotheses suggest that cognitive deficits and abnormal sleep may be connected, we are investigating the sleep-wake behavior of adult EKyn offspring. ECon and EKyn offspring were implanted with telemetric devices to acquire electroencephalogram (EEG) and electromyogram (EMG) recordings. Analyses of vigilance state-related parameters categorized as wake, rapid eye movement (REM) and non-REM (NREM) were assessed. EKyn offspring displayed reduced REM duration (–21 %) and an average duration of each REM bout (–13 %). Our data demonstrate a striking sleep deficit and impairment in hippocampal-prefrontal mediated learning and memory in offspring that were exposed to elevated kynurenine during a vulnerable period in brain development. Our future studies continue to elucidate the role of the kynurenine pathway in mediating the interplay between sleep and cognitive function.

Keywords: hippocampus, schizophrenia, sleep, kynurenic acid, nicotinic receptor

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Saturday, September 30th, 10:00 [Symposium: Models, technologies and materials used in neuromodulation]

A model and setup for opto-thermal stimulation of isolated porcine vagus nerve

Janez Rozman (1,2), Polona Pečlin (1), Samo Ribarič (2), Aicha Ibrahim Maiga (2)

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The excitation mechanism underlying infrared (IR) neural stimulation is adopted to be mediated by photo-thermal tissue transients. Since many wavelengths are capable of eliciting excitation, the wavelengths to be used should be chosen based on the desired penetration depth in the nerve tissue. It is believed that IR light-induced activation is the result of a brief (about ms) spatio-temporal temperature gradient (dT/dt and dT/dx). Accordingly, short pulses appear very effective in driving neural excitation. As a consequence, the rapid temperature rise induces a transient change in the electrical capacitance of the neuron’s plasma membrane, which in turn depolarizes the cell and induces a propagating action potential (AP). Previous work showed that mid-IR light selectively excited neural activity in myelinated and unmyelinated axons. It is also reported that it is possible to selectively and transiently inhibit electrically-initiated axonal activation, as well as to both selectively block or enhance the propagation of APs of specific motor neurons. The relatively novel technique to obtain near infrared using Light Emitting Diodes (LED) has made the equipment easier to manipulate, more accessible, and easier to operate. LED technology has provided medicine with a tool capable of delivering light deep into the nerve tissues. It was shown that pulsed, mid-IR lasers investigated as a method to stimulate neural activity have significant benefits of optically stimulating nerves over electrically stimulating, in particular the application of more spatially confined electrochemically safe neural stimulation. Accordingly, by changing IR light source parameters (e.g. pulse width and frequency), one can produce large, brief temperature transients sufficient for stimulation. In the model we use the phenomenon of water absorption of electromagnetic radiation with intra-molecular vibrational transitions in the IR region. The IR band is often subdivided into smaller sections. In this regard, we propose to use short-wave IR (SWIR) electromagnetic radiation with a wavelength below 2 microns. Precisely, the wavelength that is most effective to induce neuronal excitation is a division called short-wavelength infrared (SWIR, IR-B DIN), wavelength 1.4–3 μm. We developed several custom-designed pieces of equipment in this study, including a temperature-controlled measuring chamber, a 7 W laser source, pulse shaper providing short-wave IR (SWIR) electromagnetic radiation stimulation pulses, multi-electrode recording spiral cuff and CAP amplifier. It was adopted that the induced thermal transients have a highly localized nature and fast temporal dynamics within the particular superficial region of the porcine vagus nerve, resulting in activation patterns with high spatiotemporal resolution. The model proposes electrophysiological measurements performed on a vagus nerve removed from Slovenian male Landrace pig weighing about 70 kg, immediately after stubbing.

Keywords: neuromodulation, selective nerve stimulation, mid-infrared lasers, infrared neural stimulation, porcine vagus nerve

Saturday, September 30th, 10:00 [Symposium: Long-term impact of early life exposures and stressors on the brain: Psychopathological dimensions of mental illnesses]

Permanent alteration of cortical/hippocampal glutamate and GABA neurotransmission in adult rats following gestational cannabinoid exposure

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Cannabis or its psychoactive component ∆9-THC is the most commonly abused illicit drug by pregnant women. Despite its wide use, little is known about the long-lasting effects on the adult brain of the offspring. It has already been showed that prenatal cannabinoids exposure induces learning and memory disruption in rat adult offspring, associated with permanent alterations of cortical glutamatergic neurotransmission and cognitive deficits. The risk of long-term consequences induced by gestational exposure to cannabinoids (CBs) on hippocampal glutamatergic and GABAergic system of the offspring, has been explored. To this purpose, pregnant rats were treated daily with delta9–tetrahydrocannabinol (delta9-THC; 5 mg/kg) or the CB receptor agonist WIN55,212-2 (0.5 mg/kg). Litters from both groups were then assigned to non-exposed mothers whose pups were born on the same day. One adult (90 day-old) rat per litter from different litters per treatment group was used in each experiment. Overall, the results obtained provide evidence that maternal exposure to CBs induces an impairment of cognitive capacities in the offspring. This impairment is associated with alterations in cortical and/or hippocampal glutamate and GABA outflow, cortical neuron morphology, CB1 receptor density and hippocampal long-term potentiation. These findings suggest that maternal exposure to CBs induces long-term alterations of cortical/hippocampal glutamate and GABA systems. Although it is difficult and sometimes misleading to extrapolate findings obtained from animal models to humans, the possibility that an alteration of aminoacidergic transmission might underlie, at least in part, some of the cognitive deficits affecting the offspring of marijuana users, is supported.

Keywords: delta9-THC, microdialysis, cognition

Saturday, September 30th, 10:00 [Symposium: Models, technologies and materials used in neuromodulation]

Selective electrical stimulation and recording of an isolated porcine vagus nerve

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In the study, specific current pulses were used to stimulate Aα, Aβ-fibers and Aδ-fibers in an isolated porcine vagus nerve. The threshold and selectivity of stimulation were assessed while specific current, biphasic quasi-trapezoidal stimulating pulses were applied to the nerve via an appointed group of three electrodes within a spiral cuff, containing a matrix of ninety-nine electrodes.

To assess which nerve fibers made the most probable contribution to the compound action potential during stimulation, three components of interest, the maximum compound action potential deflection, the latency of the maximum compound action potential deflection and conduction velocity, were identified.

Results show that cuff provided both, satisfactory fascicle discrimination in selective nerve stimulation as well as satisfactory fascicle discrimination during compound action potential recording. Results also show that different stimulation intensities influenced both, the compound action potential deflection and shape. In particular, at high intensity, latency was low and corresponding conduction velocity was high. At low intensity, however, latency was high and corresponding conduction velocity was low. It could be assumed that at low intensity, large Aβ fibers having low threshold, are recruited first. As intensity increased, however, next recruited are fast B fibers. The measured compound action potentials did not show separate peaks corresponding to the A and B-fibre types.

The results would potentially contribute to better understanding of the fiber-type selective vagus nerve stimulation. In this relation, further studies will be focused to enhance the reduction of side effects of vagus nerve stimulation. Therefore therapeutic range rates in vagus nerve stimulation can be optimized and current neuroprostheses additionally improved.

Keywords: selective nerve stimulation, porcine vagus nerve fibers, conduction velocity, compound action potential

Saturday, September 30th, 10:00 [Symposium: Long-term impact of early life exposures and stressors on the brain: Psychopathological dimensions of mental illnesses]

Are offspring of mothers exposed to the ten-day war more vulnerable for mood disorders?

Liljana Šprah

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During past decades several studies provided intriguing outcomes suggesting that stressful experiences during pregnancy can negatively impact the mental health of offspring. Several behavioural and personality traits can be affected in this respect due to changes in brain neurotransmitter system and consequently increased vulnerability for depression, anxiety, schizophrenia and drug abuse. The aim of the present study was to examine the vulnerability for mood disorders in adult offspring of mothers, exposed to the ten-day Slovenian Independence War in compare to the offspring of mothers who were pregnant and gave birth before and after the war. 786 students were included in the study (60, 6 % male, 38, 9 % female) who completed self-assessment questionnaires on temperament (Temperament Evaluation of Memphis, Pisa, Paris and San Diego-auto-questionnaire version – TEMPS-A) and depression (Clinical Assessment of Depression – CAD). The men participants from the group exposed to the prenatal stress revealed more pronounced dysthymic, cyclothymic and anxious traits as well more symptoms of depressed mood, cognitive and physical fatigue and diminished interest compared to the control group of men offspring of mothers who gave birth before the war. Some differences between the sample groups were also found for female participants, even though not that pronounced. Results of this study are in line with several previous studies implying differences in vulnerability for mood disorders in offspring exposed to prenatal stress. Study outcomes also indicated that the gender of offspring exposed to prenatal stress might be associated with their vulnerability for mental health problems.

Keywords: prenatal stress, mood disorders, temperament, mental health

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Saturday, September 30th, 10:00 [Symposium: Models, technologies and materials used in neuromodulation]

Materials and technologies used in crafting of multi-electrode spiral cuffs for VNS

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Institute of Metals and Technology, Ljubljana, Slovenia

We review the methodology and technology of crafting a multi-electrode spiral cuff for fibre-type selective activation of fibers in particular superficial regions of a vagus nerve. In this relation, the design criteria and structural properties of the spot welds interconnecting platinum stimulating electrodes and stranded stainless steel lead wires, are presented. To reveal the microstructure of the weld obtained under specific welding conditions, the most advanced metallographic method of scanning electron microscopy, was used. Obtained results provide evidence that a portion of material within the spot melts without having the entire spot melt and that the chemical properties such metal’s internal resistance and its corrosive properties were not greatly affected. The resulting cuff consisted of 33 platinum electrodes embedded within a self-curling silicone spiral sheet with a nominal internal diameter of 2.5 mm to fit the size of the human cervical vagus nerve.

Keywords: spiral nerve cuff, platinum, stimulating electrode, spot welding, scanning electron microscopy

Saturday, September 30th, 10:00 [Symposium: Models, technologies and materials used in neuromodulation]

QMC-CT, a quantitative muscle assessment that patients understand and that can get them to take-home full-body in-bed gym and FES

Ugo Carraro

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Recovery from atrophy of long-term denervated muscle by h-bFES is a fact standing on sound foundations (1). Among them, a new Muscle Quantitative Color Computed Tomography (MQC-CT) (2), adds to functional and to muscle biopsy analyses, the results of tridimensional analysis of skeletal muscle. We are extending those methods to severe muscle atrophy in oldest persons, which need simplified methods of functional evaluation and rehabilitation training (3). A major problem is to convince oldest olds to continue at home volitional exercises (full-body in-bed gym) and Functional Electrical Stimulation (FES) (4). We are confident that strong evidence of structural improvements of their muscles could motivate even the more reluctant oldest persons.

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Keywords: muscle color computed tomography, severe atrophy, FES, full-body in-bed gym

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Saturday, September 30th, 10:00 [Symposium: Long-term impact of early life exposures and stressors on the brain: Psychopathological dimensions of mental illnesses]

Influence of prenatal exposure to testosterone on social behavior in Valproate mouse model of autism

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Autism spectrum disorder (ASD) is a neurodevelopmental condition diagnosed on the basis of three behaviorally altered domains: social deficit, impaired language and communication, and stereotyped and repetitive behaviors. Sexual dimorphism is one of the most consistently reported features of ASD with the ratio of male to female diagnosis approximately 4:1. The facts that male fetuses are prenatally exposed to testosterone suggest that androgen environment makes the male brain more vulnerable to different ASD risk factors. To test this hypothesis we used mice prenatally exposed to antiepileptic drug, valproic acid (VPA) that has been reported to cause autistic phenotype in rodents as well as in humans. To mimic androgen environment, pregnant females were treated with VPA alone or in combination with testosterone propionate (TP). Altogether 4 groups (control, TP, VPA, VPA+TP) of male and female offspring were screened for social and aggressive behaviors, anxiety and self-grooming. In general, the most prominent effect of the treatment was observed in mice exposed to VPA with males showing elevated aggression and females being less social than control mice. Interestingly in males, VPA and VPA+TP treatment lowered the level of anxiety like behavior while in females the same treatment caused a trend toward higher anxiety. Oxytocin in paraventricular and supraoptic nuclei showed sexual dimorphic expression with females having a higher number of cells than males. However, there were no differences in the number of oxytocin expressing cells suggesting that VPA and TP did not affect the expression of this neuropeptide. As TP treatment in addition to VPA did not aggravate ASD symptoms we suggest that androgens, at least in mouse valproate model, do not increase the vulnerability for ASD.

Keywords: autism, valproic acid, mouse, testosterone

Saturday, September 30th, 10:00 [Symposium: Models, technologies and materials used in neuromodulation]

Setup for experiments in focused pulsed ultrasound in translational biomedicine

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Pulsed ultrasound is gaining importance as an alternative to other cell stimulation techniques such as magnetic field stimulation, direct stimulation or optical stimulation. A basic setup for experiments consists of two signal generators, a high-frequency signal amplifier, an ultrasound transducer and ultrasound sensor attached to an oscilloscope. In the contribution, we will present our efforts in the development of a dedicated device which integrates all necessary devices in one single device and thus significantly improves the experiment design and experimentation processes. We will also present preliminary results on automated measurements of the pressure field from various ultrasound transducers. The developed device is particularly suitable for experiments with small animals and in vitro experiments with cells and tissue slices.

Keywords: pulsed ultrasound, focused, stimulation, device, measurements

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Saturday, September 30th, 14:30 [Symposium: Glutamate and addiction: Vulnerability traits and treatment targets]

Adolescent cocaine use perturbs glutamate synaptic maturation

Lucia Caffino

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Background: Drug addiction is a major health issue characterized by compulsive drug-seeking and taking. These behaviors often begin during adolescence, a period of significant brain development, particularly within the frontal cortex. Interfering with these processes may cause adverse consequences. While often described as a key site for compulsive drug seeking, we know little about cocaine-induced plasticity in the medial prefrontal cortex (mPFC), especially in terms of excitatory signaling.

Methods: Adolescent rats were administered cocaine from postnatal day (PND) 28 to 42 and then sacrificed at different time points following the last drug exposure. From brain regions of interest, we prepared a fraction enriched in membranes to evaluate components of the glutamate synapse.

Results: In the mPFC, the integral protein of the glutamate synapse, PSD-95, was reduced and so were some effectors of the pathways regulating spine actin network. We also found reduced dendritic spine density, with increased formation of filopodia; i.e. the immature protrusions contributing to maladaptive learning. Adolescent cocaine-exposed rats were then given a novel object recognition test to evaluate the integrity of cognitive processes. Compared to saline treated control animals, cocaine-treated rats exhibited an increased response to novelty as reflected by greater exploration. These changes were associated with a hyperglutamatergc response since PSD-95 and the metabotropic receptor mGlu5 expression were increased in cocaine-treated, but not saline-treated, rats exposed to the test.

Conclusion: We suggest that developmental cocaine administration reduces baseline glutamate activity in the mPFC, effects that may contribute to dysregulate the response to a cognitively demanding test.

Keywords: adolescence, cocaine, glutamatergic synapse

Saturday, September 30th, 14:30 [Symposium: Functional brain imaging in differential diagnosis of neurodegenerative brain disorders]

The PET perspective in early and differential diagnosis of dementia conditions

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Clinical diagnosis per se has limited diagnostic accuracy and requires the presence of cognitive symptoms, while biomarkers that are specific for pathologic phenomena would allow more accurate diagnosis when patients are in the preclinical or prodromal stage of the disease, a period that is generally held to be the best intervention time. Neuroimaging techniques may aid in the early diagnosis of neurodegenerative disorders and to clearly support the final diagnosis, through crucial biomarkers. Positron Emission Topography (PET) allows the investigation of cerebral glucose metabolism by 18F-2-fluoro-2-deoxy-D-glucose (FDG) and the quantification of protein deposition (such as Aβ amyloid and tau) through specific molecular radiopharmaceuticals. Among the included in vivo biomarkers, FDG-PET plays a key role in the identification of early brain metabolic dysfunction. Voxel-based procedures for objective image analysis can be easily applied clearly providing evidence for a role of FDG-PET in the assessment of dementia through the identification of disease-specific patterns of hypometabolism. The information provided by FDG-PET can, therefore, satisfy a fundamental need not only as a disease confirmatory test (high-sensitivity) but also as an exclusion test (high-specificity), especially in the early stage of the disease. Designing interventional strategies that target the right molecular pathways at an appropriate stage of a specific disease depends on accurate models of biomarker evolution. These must incorporate the PET biomarkers able to assess specific neuronal dysfunctions together with measures of proteinopathy burden.

Keywords: FDG-PET, radiotracers, amyloid, tau, dementia

Saturday, September 30th, 14:30 [Symposium: Glutamate and addiction: Vulnerability traits and treatment targets]

Glutamate signaling in serotonin transporter knockout rats prone to cocaine addiction

Lucia Caffino (1), Michel Verheij (1,2), Lin Que (1,2), Dewi van der Geugten (2), Chao Guo (2), Fabio Fumagalli (1), Judith Homberg (2)

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Background: Substance use disorders reflect gene x environment interactions. One factor hypothesized to affect this risk is the serotonin transporter (SERT) gene. In humans and experimental animals, inherited down-regulation of the SERT can lead to negative outcomes following exposure to adverse life events and drugs of abuse. We have investigated some of these effects in our animal models and found that rats lacking the SERT display diminished cocaine-induced serotonin responses coupled with an increased negative emotional state and increased cocaine intake under both regular (“1 hr short access”) and compulsive (“6 hr long access”) self-administration conditions. To investigate potential downstream neurobiological effects of the SERT deletion, we focused on the glutamatergic system, which transiently expresses SERT during early neurodevelopment, and is thought to be dysregulated in substance use disorders. Specifically, we focused on glutamate in the habenula, an ancient brain region beneath the hippocampus functioning as an anti-reward node and rich in glutamatergic projection neurons.

Methods: We sacrificed rats under naïve conditions or 24 hrs after the last regular or compulsive cocaine self-administration session. Using RT-q-PCR we assessed mRNA expression levels of glutamatergic genes.

Results: We found that SERT knockout rats exhibit reduced expression of glial glutamate transporters, AMPA receptors, NMDA receptors, and type 2 presynaptic metabotropic glutamate receptors (mGluR2) that regulate glutamate release. Moreover, regular cocaine self-administration decreased these features further, while compulsive self-administration led to their near-normalization.

Conclusion: SERT knockout rats might exhibit pre-existing susceptibility to addiction as they show changes in glutamate signaling that resemble those induced by drugs of abuse in wild-type animals.

Keywords: addiction susceptibility, compulsive self-administration, habenula

Saturday, September 30th, 14:30 [Symposium: Functional brain imaging in differential diagnosis of neurodegenerative brain disorders]

In vivo cholinergic basal forebrain atrophy predicts future cognitive decline in de novo PD

Chesney Craig

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Cognitive impairments are a prevalent and disabling non-motor complication of Parkinson disease, but with variable expression and progression. The onset of serious cognitive decline occurs alongside substantial cholinergic denervation, but imprecision of previously available techniques for in-vivo measurement of cholinergic degeneration limit their use as predictive cognitive biomarkers. However, recent developments in stereotactic mapping of the cholinergic basal forebrain have been found useful for predicting cognitive decline in prodromal stages of Alzheimer disease. These methods have not yet been applied to longitudinal Parkinson disease data.

In a large sample of people with de novo Parkinson disease (N = 168), retrieved from the Parkinson Progressive Markers Initiative database, we measured cholinergic basal forebrain volumes, using morphometric analysis of T1-weighted images in combination with a detailed stereotactic atlas of the cholinergic basal forebrain nuclei. Using a binary classification procedure, we defined patients with reduced basal forebrain volumes (relative to age) at baseline, based on volumes measured in a normative sample (N = 76). Additionally, relationships between the basal forebrain volumes at baseline, risk of later cognitive decline, and scores on up-to 5 years of annual cognitive assessments were assessed with regression, survival analysis and linear mixed modelling.

In patients, smaller volumes in a region corresponding to the nucleus basalis of Meynert were associated with greater change in global cognitive, but not motor, scores after 2 years. Using the binary classification procedure, patients classified as having smaller than expected volumes of the nucleus basalis of Meynert had ~3-fold greater risk of being categorised as mild cognitively impaired over up-to five years of follow up (HR = 2.76). Finally, linear mixed modelling analysis of domain-specific cognitive scores revealed that patients classified as having smaller than expected nucleus basalis volumes showed more severe and rapid decline over up-to 5 years on tests of memory and semantic fluency, but not on tests of executive function.

Thus, we provide first evidence that degeneration of the nucleus basalis of Meynert can be detected in at-risk patients even at early Parkinson’s disease stages, and that volumetric measurement of this region can predict early cognitive decline. Our methods therefore provide the opportunity for multiple-modality biomarker models to include a cholinergic biomarker, which is currently lacking for the prediction of cognitive deterioration in Parkinson disease. Additionally, finding dissociated relationships between nucleus basalis status and domain-specific cognitive decline has implications for understanding the neural basis of heterogeneity of Parkinson disease-related cognitive decline.

Keywords: Parkinson disease, cognitive function, cholinergic basal forebrain

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Saturday, September 30th, 14:30 [Symposium: Glutamate and addiction: Vulnerability traits and treatment targets]

Mapping mGluR5 changes from initial drug exposure to addiction: PET [11C] ABP688 studies in humans

Marco Leyton

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Background: The excitatory neurotransmitter glutamate has been implicated in experience-dependent neuroplasticity and drug-seeking behaviors. Type 5 metabotropic glutamate receptors (mGluR5) might play a particularly important role. In laboratory animals, mGluR5 ligands affect reward-related learning, the acquisition of drug self-administration, and the rate at which drug conditioned place preferences extinguish. In people with substance use disorders, reductions in mGluR5 availability have been observed. Since these reductions could reflect either pre-existing vulnerability traits or effects of drug use, we used positron emission tomography (PET) with the tracer [11C]ABP688 to measure mGluR5 receptor availability in emerging adults at elevated risk for addictions.

Methods: Fifty-nine participants (18–20 y.o.) were recruited from a longitudinal cohort that has been followed since birth (n = 2692). Based on externalizing traits and behaviours (e.g., impulsivity, risk-taking and aggression) during early- to mid-adolescence (11–16 y.o.) that predict future substance use problems, half of the participants were at low risk (n = 31, 20 females) while half were at high risk (n = 28, 18 females). Participants were scanned on a high-resolution research tomograph (HRRT) PET scanner with [11C]ABP688.

Results: Compared to low-risk volunteers, those at elevated risk for substance use disorders had lower [11C]ABP688 binding values in the medial orbitofrontal cortex, insula, ventral striatum, amygdala, and parahippocampus. Controlling for individual differences in alcohol use strengthened the statistical significance of the group differences.

Conclusion: Emerging adults at elevated risk for addictions have altered mGluR5 availability in cortico-limbic regions. These features might affect learning processes and increase susceptibility to acquiring drug-related behaviors.

Keywords: addiction, vulnerability, glutamate, neuroimaging

Saturday, September 30th, 14:30 [Symposium: Functional brain imaging in differential diagnosis of neurodegenerative brain disorders]

Structural network alterations and cognitive decline in Parkinson’s disease

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White matter pathways collectively form the connectome and provide the underpinnings of distributed patterns of brain activity. White matter microstructural alterations, as well as changes in the topology of structural networks, have been associated with cognitive decline in various neurodegenerative conditions. In the present study, we used diffusion MRI and graph theory-based tools to characterise structural connectome alterations in Parkinson’s disease. Measures of efficiency of network topology are reduced in Parkinson’s disease, and associated with cognitive performance. Our results provide novel information about the structural substrates of cognitive decline in Parkinson’s disease, as well as potential measures for monitoring disease progression.

Keywords: Parkinson’s disease, connectome, structural networks, diffusion MRI, cognitive decline

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Saturday, September 30th, 14:30 [Symposium: Functional brain imaging in differential diagnosis of neurodegenerative brain disorders]

Automated differential diagnosis of parkinsonian syndromes using FDG-PET image analysis

Tomaž Rus

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Background: Differentiating among parkinsonian syndromes is based on clinical criteria, which may be challenging early in disease course. Final diagnosis can only be confirmed at autopsy. While structural neuroimaging does not add additional information in early disease stages, the specific metabolic brain changes evaluated by FDG-PET imaging can improve the diagnostic accuracy. Disease specific metabolic brain patterns were identified for PD, MSA, PSP. A probabilistic algorithm for the diagnostic classification based on the expression of various metabolic covariance patterns was developed previously.

Aim: The aim of our study was to compare the diagnosis of parkinsonian patients made by automated spatial covariance analysis of FDG-PET images with the clinical one, which was made by a “blinded” neurologist two years after the FDG-PET imaging.

Methods: Ninety-four patients with parkinsonism (PD, MSA, PSP) (age 68.8 ± 9.1 years, mean disease duration 4.9 ± 3.5) and 20 healthy controls (age 67.2 ± 5.7 years) underwent FDG-PET brain imaging. Clinical diagnosis was made in 56 patients based on clinical examination and in 38 cases based on their last medical records.

Results: Among 94 patients, 68 were clinically diagnosed as having PD, 12 – MSA and 14 – PSP. Based on an automated algorithm, 57 patients were identified as having PD, 7 – MSA, 17 – PSP and in 14 cases were indeterminate. Algorithm achieved 92 % specificity and 97 % positive predictive value in differentiation among PD, MSA and PSP.

Conclusion: Automated analysis of metabolic patterns evaluated by FDG-PET images may help in differentiation of parkinsonian syndromes in their early stages.

Keywords: FDG-PET, metabolic brain pattern, automated algorithm, parkinsonism

Saturday, September 30th, 14:30 [Symposium: Glutamate and addiction: Vulnerability traits and treatment targets]

mGlu5 receptors and extinction of drug seeking

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Both pharmacological and genetic approaches confirm that mGlu5 receptors are implicated in the rewarding properties of various drugs and the integration of reward-related cues. This latter issue prompted further investigation into the role of mGlu5 in extinction of reward-seeking. Using mGlu5 knockout (KO) mice, we have shown a critical role for mGlu5 in the extinction of cocaine-driven behaviours. These data suggest a role for mGlu5 in regulating contextual salience. The role of mGlu5 signalling in drug context memories was further studied in rats trained to self-administer cocaine. Rats were subjected to context extinction sessions or passive withdrawal in their home cage. MTEP (2 mg/kg i.p.) or vehicle was administered immediately after each context extinction session. Context extinction had a “protective” effect, reducing drug-primed reinstatement compared to abstinence; however, this was attenuated by MTEP. Similar studies also implicated mGlu5 signalling in the extinction of drug cues. Collectively, these findings suggest that extinction of contextual associations and cue salience involves mGlu5 signalling. This has important implications for developing more effective behavioural therapies for promoting abstinence and preventing relapse in drug-dependent individuals.
Keywords: mGlu5, exticntion, relapse

Saturday, September 30th, 14:30 [Symposium: Functional brain imaging in differential diagnosis of neurodegenerative brain disorders]

Different FDG-PET metabolic patterns in parkinsonian syndromes

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Aim: Using 18F-FDG-PET and specific network analysis our aim was to identify and cross-validate a characteristic metabolic brain network associated with Parkinson’s Disease (PD) in Slovenian population: PD Related Pattern (PDRP-Slovenia).

Methods: The pattern was identified analyzing 20 PD patients and 20 normal controls (NC) and validated in an additional cohort of 20 PD and 20 NC subjects. The analysis was performed using Scaled Subprofile Mapping/Principal Component Analysis method. Specific patterns of other neurodegenerative syndromes: multiple system atrophy and progressive supranuclear palsy were identified using the same network analysis, too.

Results: PDRP-Slovenia is characterized by hyper and hypoactivity brain regions that are functionally related to each other. Hyperactive regions are: pallidum, putamen, thalamus, brain stem, and cerebellum and are associated with hypometabolism in sensorimotor cortex, posterior parietal, occipital and frontal cortices. The expression of PDRP network can be measured in each individual subject and his/her “subject score” calculated. The PDRP was found to be significantly more expressed in PD patients than in NC, MSA or PSP subjects. We additionally studied the effect of different image reconstruction algorithms on PDRP network topography, its ability to discriminate PD patients from healthy controls and from other neurodegenerative syndromes.

Conclusion: We may conclude that PDRP is a reliable biomarker of Parkinson’s disease, unaffected by the reconstruction algorithms, which may vary across different scanners and centers worldwide.
Keywords: Parkinson’s disease, differential diagnosis, FDG/PET, network analysis, image reconstruction algorithms

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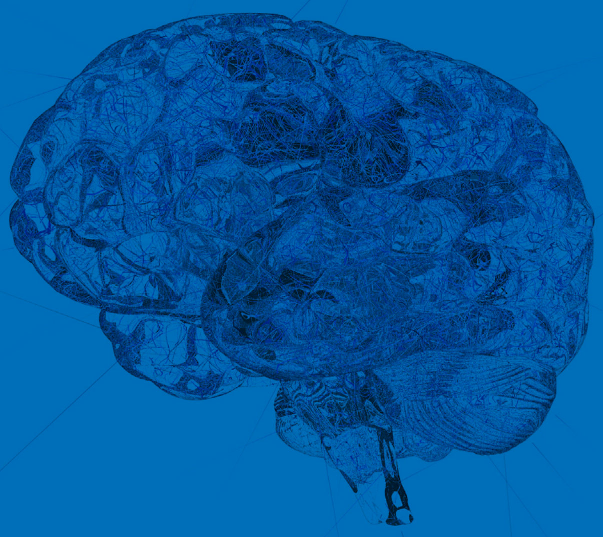

Abstracts

SNC'17 Posters

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Faculty of Medicine, Ljubljana, Slovenia
29–30 September 2017

CEL.01 Friday, September 29th, 13:00 [Poster section: Cellular neuroscience A]

RNA foci, transcribed from C9ORF72 expansion, form intranuclear paraspeckle-like bodies

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The expansion of the GGGGCC repeat in the gene C9ORF72 is the most common genetic cause of FTLD and ALS. It is transcribed both from the sense and antisense strands leading to the formation of nuclear RNA foci, which sequester specific RNA binding proteins and affect various steps of post-transcriptional gene regulation. Here, we show that the core paraspeckle proteins SFPQ, NONO and PSPC1 bind to (G4C2)n repeat RNA in vitro, and colocalize with nuclear RNA foci in transfected cells and brain tissue of C9ORF72 mutant carriers at post-mortem. Sense RNA foci lead to an increased number of SFPQ-stained subnuclear bodies, which form independently of the known paraspeckle platform long non-coding RNA NEAT1. Furthermore, (G4C2)72 RNA foci also colocalized with paraspeckle-associated associated Alu repeat-containing RNAs hLincRNA-p21 and Prss35, indicating that (G4C2)n RNA foci might replace NEAT1 as a scaffold of paraspeckle-like structures. Our results show that (G4C2)n RNA foci form paraspeckle-like structures, which function in similar fashion as paraspeckles and modulate nuclear compartmentalization of paraspeckle-bound RNAs.

Keywords: ALS, FTLD, C9orf72, RNA foci, paraspeckles

CEL.03 Friday, September 29th, 13:00 [Poster section: Cellular neuroscience A]

Lateral fluid percussion injury induces astrocytosis and microgliosis without a neuronal loss in the rat frontal cortex

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Traumatic brain injury (TBI) affects many brain regions but those more distant to the impact site have been poorly studied. Therefore, the purpose of this research was to determine the changes of the neurons, astrocytes and microglial cells in the frontal cortex at different time points following experimental TBI.

TBI of moderate severity was induced over the left parietal cortex in adult male Wistar rats by using the lateral fluid percussion injury (LFPI) method. Sham-operated animals were used as the control group. Rats were sacrificed 1, 3 or 7 days after the injury or sham procedure and their brains were prepared for the immunohistological analyses. NeuN, GFAP and Iba1 antibodies were used as the markers for neurons, astrocytes and microglial cells, respectively.

Significant astrocytosis and microgliosis were detected at day 7 after the injury while the number of neurons in the rat frontal cortex was not significantly changed in any of the investigated time points after the brain trauma.

Our study showed marked inflammatory response and no neuronal loss in the frontal cortex, the brain region distant from the primary impact site, in the first week following the LFPI in the rat.

This work was supported by the University of Rijeka under Project No. 13.06.1.1.09 to Gordana Župan

Keywords: inflammation, lateral fluid percussion injury, frontal cortex, neuronal loss, rat

CEL.05 Friday, September 29th, 13:00 [Poster section: Cellular neuroscience A]

The mechanism of folding and trafficking of the human dopamine transporter (hDAT) and its mutants associated with infantyle parkinsonism-dystonia

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Medical University of Vienna, Austria

Background: Dopamine transporter (DAT), is responsible for sequestering released dopamine from the synaptic cleft. Folding-defective mutants of the human dopamine transporter (hDAT) cause a syndrome of deficiency infantile parkinsonism-dystonia (IPD).

Methods: We created 13 mutations responsible for IPD. HEK293 cells were transiently co-transfected with plasmids encoding the wild-type dopamine transporter and IPD mutants. Radioligand dopamine uptake, confocal laser scanning microscopy and immunoprecipitation experiments were performed 48 h after transfection to study the pharmacochaperonig effect on folding of wild type and mutant DATs.

Results: Confocal microscopy experiments indicated that all 13 mutated DATs were retained in intracellular compartments, namely in the ER. Regarding their functional activity, none of the mutants showed any appreciable dopamine uptake compared to the wild type DAT. Interestingly, 3 of the mutants could be functionally rescued, i.e. they responded to treatment by pharmacological chaperones, noribogaine and pifithrin-μ (an inhibitor of the heat shock protein HSP70. Pretreatment of cells with noribogaine and pifithrin-μ is predicted to reduce the association of hDAT mutants with calnexin and HSP70-1A. In addition, experiments were also done to examine these effects in flies (Drosophila melanogaster) carrying the IPD hDAT mutations. We rescued two mutants (V158F and G327R) in vivo. In the case of L368Q, flies were not able to hatch due to unknown reasons.

Discussion: The current research work not only provides a systematic in vitro and in vivo approach for screening IPD-causing DAT mutants but also consolidates the fact that pharmacochaperoning can be used to remedy disease-causing folding deficiencies in SLC6 transporters.

Keywords: dopamine, dopamine transporter, pharmacochaperoning

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CEL.07 Friday, September 29th, 13:00 [Poster section: Cellular neuroscience A]

Innervation of primary human skeletal muscle cells induces isoform-specific upregulation of Na+/K+-ATPase subunits

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The abstract has been removed on the request of the author.

Keywords: Na+/K+-ATPase, FXYD1, innervated primary skeletal muscle cell, FXYD5

CEL.02 Saturday, September 30th, 13:00 [Poster section: Cellular neuroscience B]

Role of astrocytes in survival of carbon monoxide-intoxicated neuronal cells, treated with hyperbaric oxygen

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Carbon monoxide (CO) is the leading cause of poisoning-related deaths and 3–40 % CO poisoning survivors develop delayed and sometimes permanent neurological sequelae due to neuronal and glial apoptosis. The dilemma concerning the usefulness of hyperbaric (3 bar) oxygen (HBO) treatment in CO-poisoned patients is still of current interest. It has already been proven that HBO reduces apoptosis in CO-exposed astrocytes. Due to the central role of astrocytes in maintaining neuronal function we investigated the hypothesis that HBO therapy by preserving the viability and neurotrophic activity of astrocytes may exert a beneficial effect on acute CO poisoning-induced impairment of neuronal cells as well.

Exposure of rat cortical neurons in primary culture alone or co-cultured with astrocytes to 3000 ppm CO followed by 24 h of normoxia revealed a time-dependent decline in viability, ATP concentration and mitochondrial dysfunction accompanied by caspase-8, -9, -and -3/7 activation in both cell cultures. 1 h HBO treatment disclosed significant differences in providing mitochondrial protection and prevention of pro-apoptotic processes. While in neuronal/astrocyte co-culture time-dependent protective effect of 100 % oxygen was evident, in neuronal culture HBO exhibited no profound benefit in CO-induced mitochondrial impairment and apoptosis prevention. Moreover, HBO itself affected viability and triggered several cysteine proteases in neuronal cell culture but not in co-culture.

CO and HBO-induced deleterious neuronal effects are not present when neurons and astrocytes are co-cultured thus suggesting astrocytes to have a key role in supporting survival and function of neurons after acute CO poisoning and HBO treatment.

Keywords: carbon monoxide toxicity, neuronal culture, apoptosis

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CEL.04 Saturday, September 30th, 13:00 [Poster section: Cellular neuroscience B]

TDP-43 expression in the parietal cortex and the hippocampus following a single traumatic brain injury in the mouse

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TAR DNA-binding protein-43 (TDP-43) is recognized as one of the main disease-associated proteins in many neurodegenerative diseases and recent data indicate that it also could be included in a complex cascade of different pathophysiological processes initiated by traumatic brain injury (TBI). The aim of this study was to investigate the intracellular localizations of the TDP-43 in different types of the brain cells in the parietal cortex and the hippocampus in experimental TBI.

Single moderate lateral fluid percussion injury (LFPI) was performed over the left parietal cortex in adult male C57BL/6 mice. Animals were sacrificed 3 or 14 days after the LFPI and their brains were prepared for immunohistological analyses. Sham-operated animals were used as the control group. Brain slices were double-stained with TDP-43 antibody together with antibodies against specific neuronal, astrocytic or microglial markers.

TDP-43 nuclear expression was detected in all mentioned cell types of both investigated brain structures in all injured animals. TDP-43 cytoplasmatic localization was found in the neurons and the microglia of the parietal cortex at 3 and 14 days after TBI, while no such changes were observed in the hippocampus. Our preliminary study suggests that even a single moderate TBI can be associated with the changes in the intracellular localization of the TDP-43 immunoreactivity, in the neurons and the microglial cells of the parietal cortex in the mouse.

This work was supported by the University of Rijeka under Project No. 13.06.1.1.09 to Gordana Župan

Keywords: TDP-43, parietal cortex, hippocampus, traumatic brain injury, mouse

CEL.06 Saturday, September 30th, 13:00 [Poster section: Cellular neuroscience B]

An approach to study cholesterol-rich domains in the outer leaflet of the plasma membrane of pituitary lactotrophs

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The release of neurotransmitters and hormones involves many steps, including the fusion of secretory vesicles with the plasma membrane. Following the merger of opposing membrane bilayers, a fusion pore is formed, through which vesicle cargo can exit. The fusion pore consists of highly curved membrane regions, which are likely built by anisotropic lipids, such as cholesterol. To learn whether cholesterol-rich membrane domains are associated with the merger of the vesicle and the plasma membrane the following analysis approach was introduced. Cultured pituitary lactotrophs were labeled with anti-prolactin (PRL) antibodies and with the novel cholesterol-binding fluorescent marker D4-perfringolysin-mCherry (D4-PFO) and imaged using structured illumination microscopy. Then a ~800nm wide membrane region band was generated by image processing and the intensity threshold was calculated using automated algorithms for both channels. Above threshold fraction of pixels allowed the calculation of relative D4-PFO-positive membrane area and the measurements of a minimal distance between D4-PFO- and PRL-positive structures. Additionally, the diameter of PRL-positive granules was evaluated to test whether the association between the two signals was a function of vesicle cargo size. Preliminary results revealed that in lactotrophs exposed to 50 mM K+, the area of D4-PFO-positive regions in the outer plasma membrane leaflet and the association between D4-PFO and PRL-containing granules decreased, while the minimal D4-PFO-to-PRL distance increased. Overall, these results suggest that cholesterol is redistributed during regulated exocytosis and that the implemented approach can be further used in studies of cholesterol distribution in inner membrane leaflet.

Keywords: regulated exocytosis, cholesterol-rich domains, perfringolysin, structured illumination microscopy, prolactin

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CLI.01 Friday, September 29th, 13:00 [Poster section: Clinical neuroscience A]

Connective tissue dysplasia in young person: psychophysiological assessments and manual dexterity

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In the general structure of diseases of the musculoskeletal system, non-inflammatory diseases of the joints, which include connective tissue dysplasia, take the leading place. However, if the study of the pathogenesis and treatment of osteoarthrosis, the most common non-inflammatory disease of the joints of older persons, is devoted a lot of work, then noninflammatory diseases of the joints of young people are studied less. One way to determine DST is the Beighton scale, based on the detection of hypermobile syndrome (Beighton R., 1988). The features of the psycho-functional state and the motor skills of the fingers in young people with signs of connective tissue dysplasia were investigated (6–9 points on the Beighton scale). It was found that connective tissue dysplasia is accompanied by vagotonia and hyposthenic body type. The psychological dimensions of activity and mood according to the SAM (state of health, activity, mood) questionnaire were reduced and the aggressiveness index dysplasia. In the presence of symptoms connective tissue dysplasia, it was observed the disturbance of a fine motor skill such as the low differentiation of the finger movements, the rigidity of the fingers and the marked decrease in the involvement of the thumbs of both hands in the general motor activity of the hand. Our results are consistent with the data of the authors who showed the association between hypermobile syndrome and osteoarthrosis of the phalangeal and knee joints (R. Moskowitz, W. Roland, 2006). Thus, connective tissue dysplasia is characterized by autonomic disorders, which can be associated with neurocirculatory asthenia, which is formed due to the fact that the hypothalamic-pituitary-adrenal system and connective tissue are laid simultaneously in embryogenesis. The revealed disturbances of the psycho-functional state and the peculiarities of the fine motor skills of persons with signs of connective tissue dysplasia can be regarded as an indicator of resource depletion in adaptation to stress, and their severity has a certain parallelism with manifestations of somatic markers of connective tissue dysplasia.

This work was funded by the subsidy allocated to the Kazan Federal University for the state assignment in the sphere of scientific activities 17.9783.2017/8.9.

Keywords: connective tissue dysplasia, manual dexterity, psycho-functional state

CLI.03 Friday, September 29th, 13:00 [Poster section: Clinical neuroscience A]

Crossed cerebellar diaschisis detected with BOLD MRI cerebrovascular reactivity

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Introduction: Crossed cerebellar diaschisis (CCD) describes the reduction of cerebellar blood flow and metabolism contralateral to a supratentorial lesion and is related to poorer clinical outcome. Currently, Positron Emission Study (PET) imaging is used to determine the presence of CCD: However, recently the use of BOLD cerebrovascular reactivity (CVR) has been suggested. We aim to quantitatively measure cerebellar BOLD-CVR and relate these findings to PET derived cerebral blood flow.

Method: We investigate subjects with symptomatic unilateral neurovascular steno-occlusive disease. CBF was measured by 15-H2O-PET before and after an acetazolamide challenge. BOLD-CVR was measured using a controlled iso-oxic hypercapnic CO_2 stimulus. CCD was determined visually based on the PET images. For both PET-CBF images, a cerebellar asymmetry index (CAI: (ipsilateral – contralateral hemisphere)/ ipsilateral hemisphere) was determined. As outcome measurements, initial clinical status (NIHSS – and mRS-Score) were compared as well as 3-months post-stroke.

Results: We included 19 patients (CCD: 7 (36 %)). In CCD+, CVR in the CCD+ cerebellar hemisphere was significantly decreased (0.16 vs. 0.19, p &lt; 0.05). No cerebellar differences were found in the CCD- subjects. The PET-CAI did not differ between both PET images(CCD+: 7.04 ± 1.75 vs. 7.19 ± 1.46, p = 0.6; CCD-: 1.08 ± 3.74 vs. 0.32 ± 2.87, p = 0.4) which indicates a preserved CBF reactivity. Significant differences between CCD+ and CCD- group were seen in both clinical scores at admission (CCD+ vs. CCD-: NIHSS: 5.86 vs. 1.46, p &lt; 0.01; mRS: 2.86 vs. 0.92, p &lt; 0.01) and after 3 months (NIHSS: 2.83 vs 0.33, p = 0.01; mRS: 1.33 vs. 0.27,p = 0.03).

Conclusion: BOLD-CVR demonstrated a good agreement with PET and can, therefore, be used to detect CCD, which is related to worse clinical status and outcome.

Keywords: BOLD, cerebrovascular reactivity, blood flow imaging

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CLI.05 Friday, September 29th, 13:00 [Poster section: Clinical neuroscience A]

Influence of transcutaneous electrical stimulation of the spinal cord on vegetative regulation of cardiac activity

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In the literature, there are ambiguous data on the effect of transcutaneous electrical stimulation of the spinal cord (tSCS) on cardiac activity. In order to predict (and to correct) unnecessary changes in autonomic functions that may accompany correction of motor disorders, it is necessary to consider the mechanisms of changes in autonomic functions under the influence of tSCS. As is known, the activity of regulatory mechanisms for controlling the circulatory system is manifested in cardiointervals variability. The purpose of this study was to study the variability of a heart rate after tSCS for 1 minute at 30 Hz with a pulse duration of 1 ms at T11–12 vertebrae in healthy subjects. After tSCS stimulation, we observed a decrease of the mean heart rate (M) and an increase of the standard deviation (SDNN). Prior to the stimulation in terms of the mode (Mo) and variation span (MxDMn), subjects were rated for normotonic, and after tSCS, the vegetative activity was assessed as vagotonic. tSCS didn’t cause an increase in sympathetic influences: there was no increase in Mode Amplitude (MoA), and the stress index after tSCS decreased. Thus, tSCS at the lower thoracic level increases the degree of cardiointervals variability, which indicates an increase in parasympathetic tone. This suggests that the application of this method leads to an increase in processes of self-regulation and activation of autonomic regulation of the rhythm of the heart.

This work was funded by the subsidy allocated to Kazan Federal University for the state assignment in the sphere of scientific activities №17.9783.2017/8.9.
Keywords: transcutaneous electrical stimulation, cardiointervals variability, vegetative regulation

CLI.02 Saturday, September 30th, 13:00 [Poster section: Clinical neuroscience B]

recoveriX – Brain-computer interface controlled avatar and functional electrical stimulation: clinical study for motor function rehabilitation after stroke

N. Murovec, W. Cho, R. Ortner, C. Guger

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BCI with detection of neuronal activity controls the external devices to provide appropriate sensory feedback from peripheral nervous system to central nervous system (CNS). With multiple training sessions when the feedback is sent to CNS according to the motor intention, the neuronal network in the brain can reorganize due to neuroplasticity. In this current study, a BCI controlled avatar and functional electrical stimulation (FES) is used to provide the visual and proprioceptive feedback following the linear discriminant analysis and common spatial filter classifying the brain activity acquired by EEG. Only upon correct classification avatar and FES are triggered. The training was designed having 25 sessions (240 trials of either left or right motor imagery) of BCI feedback sessions over 13 weeks. Before and after the BCI training intervention six clinical measures are used to observe motor improvement. The primary measure is upper extremity Fugl Meyer assessment, following modified Ashworth scale, Fahn tremor rating scale, Barthel index, 9 hole peg test and Box and Blocks test. In between the training 9-HPT and BBT are used to assess the improvement. One of the stroke patients who participated in the training shows promising results with UE-FMA score going from 25 to 46 points. Before the 18th training session, he could not complete the 9HPT and following that he was able to finish it in 10 mins 22 secs and after the 25th session in 2 mins 53 secs. Group study with 50 patients including a control group with FES only will be finished soon.

Keywords: brain-computer interface, stroke rehabilitation, motor imagery

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CLI.04 Saturday, September 30th, 13:00 [Poster section: Clinical neuroscience B]

Vascular physiology of CO_2: impact on cerebrovascular reactivity and neurovascular coupling

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Introduction: Neurovascular coupling describes the cascade between neuronal activity and subsequent signal increase seen on functional MRI (fMRI). These fMRI signal changes can be negatively influenced in brain areas exhibiting impaired Blood Oxygenation-Level Dependent cerebrovascular reactivity (BOLD CVR). Controlled BOLD CVR studies have commonly been performed using a calibrated preset carbon dioxide (CO_2) baseline for all subjects, but recent data suggests that this may influence CVR readings. We therefore prospectively included 20 healthy subjects.

Methods: Ten subjects were scanned at resting CO2 (group A) and 10 at a preset isocapnic CO2 baseline (±40 mmHg; group B). Whole brain BOLD CVR was measured using precise standardized changes in CO2. fMRI volumes were acquired during a calibrated bilateral finger-tapping task.

Results: Whole brain CVR was significantly decreased for group B (group A 0.26 ± 0.05 vs group B 0.16 ± 0.05, p &lt; 0.001). For the hand area in the bilateral precentral cortex, both CVR and Δ% fMRI (= fingertap signal) were lower for group B (group A 0.20 ± 0.04 vs group B 0.13 ± 0.05, p &lt; 0.01; 1.19 ± 0.31 vs 0.62 ± 0.37, p &lt; 0.01) and were highly correlated (r = 0.72, r2 = 0.53).

Conclusion: CVR and fMRI fingertap studies performed at a preset ‘normocapnic’ CO_2 baseline result in significantly decreased values as opposed to measurements taken from a subjects’ own resting CO_2.

Keywords: BOLD, fMRI, neurovascular coupling

COG.01 Friday, September 29th, 13:00 [Poster section: Cognitive neuroscience A]

The peculiarities of brain activation during delayed visual recognition: fMRI-study

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Purpose: The peculiarities of activation of brain structures were investigated during involuntary remembering.

Methods: Eight healthy right-handed subjects (mean age – 21.8) participated in the study. The experiment consisted of two sessions. In the first one subjects should categorize stimuli presented on the screen as animated and non-animated. In the second session undertaken averagely in 42 hours in fMRI-tomograph, subjects should answer, if they had seen a presented stimulus in the previous session or not. fMRI data were acquired using 3T Siemens Verio and T2*-weighted echo planar imaging (TR = 2200 ms, TE = 25 ms, flip angle = 90, FOV = 192x192 mm). fMRI analysis was conducted in FSL 5.0 (Z &gt; 2.3, a corrected cluster threshold of p = 0.05).

Results and Conclusion: Significant activation of the following structures was revealed: the left parahippocampal gyrus, the left putamen and the bilateral anterior cingulate gyrus. We can put forward a hypothesis that delayed visual recognition is a process which demands not only retrieval of information from episodic memory, but also detecting new stimuli (this, probably, is connected with activation of the putamen) and high cognitive control (this is why the anterior cingulate gyrus is involved in this task). This data supports our previous results (Kozlovskiy, Neklyudova et al., 2016) where dipole source localization was used for the similar experiment and activation of the same structures was shown.

Keywords: visual recognition, episodic memory, fMRI

COG.03 Friday, September 29th, 13:00 [Poster section: Cognitive neuroscience A]

Regulation of brain activity with neurofeedback in ADHD children

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Neurofeedback (NF) is a type of biofeedback that uses real-time displays of brain activity, or some kind of its correlates, to teach self-regulation of brain function. It is associated with behavioural, cognitive and academic gains. Thanks to NF, individuals can learn to alter their typical EEG pattern to one that is consistent with a focused, attentive state. This has been suggested to be particularly useful in subjects affected by Attention-Deficit/Hyperactivity Disorder (ADHD). ADHD is a brain disorder marked by an ongoing pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. NF is considered as the most promising non-medication approach and has the added advantage that the results take a long time to disappear when training stops. The most common pattern of EEG activity found in ADHD is the excess of theta waves in the frontal region. There can also be the excess of alpha or reduction of beta activity.
We performed 10 NF sessions in four ADHD children (8–12 years), clinically diagnosed, 2 times a week for 5 weeks. The Mindwave cup (Neurosky, one frontal electrode and wireless connection with the main PC) and the games FocusPocus and Kidzen were used.
A 21-led Quantitative-EEG was done before and after the training period.
In three out of the four children changes were observed in the QEEG after the training period: a reduction of the frontal theta activity and a less pronounced reduction of frontocentral alfa activity, which became more posterior. These preliminary results seem to confirm a regularization of the brain activity after NF in ADHD children.

Keywords: neurofeedback, ADHD, reduction of theta activity

COG.05 Friday, September 29th, 13:00 [Poster section: Cognitive neuroscience A]

Acute effects of dominant or submissive body pose adoption on thermosensitivity and pain threshold

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The goal of our research was to determine if an instructed brief adoption of a dominant or submissive body pose influences subjects’ sensitivity to temperature change and their threshold for thermal pain.

Effective dominant and submissive poses were selected through a web-based survey, where participants had to briefly adopt one of six specified poses and subsequently rate how each pose made them feel. The highest rated dominant and submissive pose was used in the present study where sensitivity to temperature change and thermal pain threshold were assessed in healthy volunteers prior to and after adoption of a randomly assigned pose. Thermode of a commercial Medoc Pathway PSES device was placed on the dominant hand’s thenar. In temperature change detection test, temperature gradually changed from neutral to warm or cold and subjects had to report the first detected change and its direction. In thermal pain threshold measurements, participants were told to press the button as soon as the thermal stimulus reached a painful level, which immediately reset the thermode temperature back to neutral.

After initial baseline thermosensorymetric assessment, a voice recording guided subjects into a proper adoption of a randomly assigned pose three consecutive times for twenty seconds. Immediately thereafter thermosensitivity was assessed again. Using standardised questionnaires participants rated how powerful/powerless the adopted pose made them feel, and gave an estimate of their own dominance/submissiveness.

Preliminary results indicate that both dominant and submissive pose adoption affected sensitivity to temperature change, while only the dominant pose adoption acutely increased thermal pain threshold.

Keywords: embodied cognition, nonverbal communication, power posing

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COG.07 Friday, September 29th, 13:00 [Poster section: Cognitive neuroscience A]

The influence of emotional stimuli on P3 in an »oddball« paradigm

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Attention allows us to direct our limited processing capacities to the selected stimuli while ignoring irrelevant ones. Stimuli that are motivationally important and crucial for adapting to one’s environment automatically capture attention. Oddball paradigm is widely used in event-related potential (ERP) research of attention. The task of the participant is to identify rare target stimuli and ignore frequent standard and rare distractor stimuli. Attending to targets elicits ERP called P3 with a peak at around 300 ms. Previous research has shown that emotional stimuli alter P3 component. The aim of our study was to investigate how the P3 is affected by the event (target, distractor), affective valence of the stimulus (neutral, negative) and the type of appraisal (affective, nonaffective). Target and distractor stimuli were pictures from affective pictures databases (IAPS, NAPS, GAPED) which differ over their affective valence (neutral, negative) and content (human, nonhuman). Their scrambled versions were used as standard stimuli. In each of the four conditions targets were different - negative, neutral, human or nonhuman pictures. The participants were instructed to press one button for targets and another one for any other stimuli. During the task, EEG signal was recorded with 64-channel actiCAP system. Participants also filled out the Zuckerman-Kuhlman Personality Questionnaire (ZKPQ), the Reinforcement sensitivity theory of personality questionnaire (RST-PQ), which both assess affective and motivational aspects of personality, and the Kentucky Inventory of Mindfulness skills (KIMS). Differences in P3 across conditions (negative vs. neutral, human vs. non-human) and correlations between P3 and personality measures will be presented.

Keywords: emotion, P3, oddball

COG.09 Friday, September 29th, 13:00 [Poster section: Cognitive neuroscience A]

Comprehensive understanding of instrumental description of psychophysically elicited somatosensory (pain) perceptions

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Pain, a submodality of somatic sensations, represents physiological, psychical and other experiences and processes. This multidimensional phenomenon depends on the context and meaning of the information as well as on the person’s own unique past experiences, current cognitive and emotional state, and future expectations. The subject has to be aware of the sensation and report its cognitive (conscious, mental) interpretation, i.e. perception. Her/his own perceptions could be entirely instrumentally processed. The instrumentally psychophysically elicited responses need the comprehensive understanding and explanatory description (cognitive interpretation).

The purpose of study has been the characterization of the instrumentally determined and subjectively described subject’s own perceptions.

We have examined 250 patients with 5 different diagnoses (toxic and diabetic neuropathy, phantom pain, restless leg syndrome and Sjögren’s syndrome). Instrumental psychophysical examination was performed using precise, computer-controlled devices: TSA-II – NeuroSensory Analyzer and Thermotes. The sophisticated instruments generate highly repeatable natural sensory stimuli (i.e. thermal and vibratory stimuli, such as warmth, cold, heat-induced pain, cold-induced pain), and document the elicited responses. Subjects simultaneously describe their own unique perceptions.

Instrumentally documented responses and subjectively perceived and reported modalities have been compared with 38 previously determined and generalised phenotypic patterns. The perceived modalities have been classified as physiologic (i.e. 4 thermal: cold, warmth, cold-induced pain and heat-induced pain) or 34 pathologic (i.e. hypoesthesia, allodynia etc.).

Conscious understanding of comprehensive information explains the instrumentally psychophysically elicited somatosensory (pain) perceptions. The recognition of phenotypic pattern helps to identify underlying pathophysiological mechanisms and even facilitates effective management and rehabilitation.

COG.04 Saturday, September 30th, 13:00 [Poster section: Cognitive neuroscience B]

Why accountants compromise on their fiduciary duties: fMRI evidence on the role of the human mirror neuron system

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Accountants who are entrusted the integrity of financial reporting often feel empathy for employees and managers whose personal interests are affected by financial reports. In this study, we investigate how the ability to suppress empathy is associated with the activity of human mirror neuron system (Rizzolatti &amp; Craighero, 2004). We conducted a functional magnetic resonance imaging (fMRI) study using 30 experienced accounting and finance managers in business firms in Slovenia (15 male, age M = 37.03, range = 24–52 years; work experience M = 12.77, range = 1–26 years). The participants’ empathy reflected in varying tolerance to misreport was measured using behavioural scenarios (Eskenazi, Hartmann &amp; Rietdijk, 2016) in which they were induced to misreport by revealing them the adverse effects of financial reports on employees’ personal circumstances. The activity of mirror neuron system was estimated by measuring participants’ brain activity while they were passively observing series of short videos of facial expressions showing disgust, anger, joy, surprise, and neutral expression, and rotating objects. Estimates of mirror neuron system activation will be correlated with the results on misreporting to test the hypothesis that individuals with higher emphatic response — as indexed with mirror neuron system activation — tend to be more susceptive to emotional pressure.

Keywords: accountants, empathy, mirror neuron system, fMRI

COG.06 Saturday, September 30th, 13:00 [Poster section: Cognitive neuroscience B]

Neural coding mechanisms underlying spatial working memory

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Spatial working memory refers to the temporary retention of spatial information in the absence of perceptual input. The most consistently observed neural correlate of working memory is the persistent neural activity in prefrontal and posterior parietal cortices that occurs during a delay from a sensory cue to the contingent motor response. However, the nature of the code carried by this neural activity is unknown. In the case of spatial working memory tasks, the neural activity may represent the preceding positional information of a stimulus (i.e. retrospective sensory code) or the direction of a succeeding motor response (i.e. prospective motor code). To address this issue, we conducted a study with 31 healthy subjects that underwent functional magnetic resonance imaging, while they were performing a spatial working memory task, where subjects were biased towards or against the use of the prospective motor code. Specifically, participants were presented with a brief target stimulus and after 10 s delay period asked to make a motor response to the position of the target using a joystick, where the response direction was either predictable or unpredictable. We characterised localisation of neural activity triggered by the spatial memory task and identified differences between task conditions with different hypothesised coding mechanisms.

Keywords: spatial working memory, fMRI, prefrontal cortex

COG.08 Saturday, September 30th, 13:00 [Poster section: Cognitive neuroscience B]

Transdisciplinary approach to comprehensive explanation of psychically modulated sensory (pain) information

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Perceptions (i.e. cold, warmth and pain) are highly subjective, multidimensional experiences of sensory (pain) information, which define e.g. current emotional status, past experiences, fear, stress, nociception. The contemporary transdisciplinary approach integrates multiple scientific, professional and practical dimensions into a comprehensive knowledge of pain. Sensory experiences are currently recorded with methods and techniques that provide limited information regarding comprehensiveness (nociception, cognition, emotions etc.). Psychical processes (psychological management) are able to modulate knowledgeable somatosensory (pain) perceptions.

We present individualised/person-oriented comprehensive cognitive approach that involves both, biological/physiological and mental/cognitive processes. Patterns of perception modalities have been used for identification of modulatory effect and psychically modulated somatosensory (pain) perceptions.

We tested 3346 subjects. Normal/normative perceptions and sensory alternations, elicited with thermal specific (cold, warmth) and thermal pain (cold pain, heat pain) stimuli, were collected. Instrumental determination was performed using psychophysical instruments, the TSA-II – NeuroSensory Analyzer and Thermotest.

The reported somatosensory perceptions are expressed by 4 physiologic (“normal/normative”) and 34 altered (pathologic) psychophysical recognition symptoms and signs (descriptors).

The recognition of pain and other very subjective somatic perceptions is mandatory for their proper interpretation. Accurate interpretation of results requires an understanding of a complicated system, where physiological components, sensation and perception, are modulated by psychical influences too. Psychophysically determined changes could be appreciated as a far more accurately, repeatedly and consistently validated measure with predictive potentials. Somatosensory thermotest repeatedly confirms its importance as a means of recognizing abnormalities in most of somatosensory (temperature and pain) perceptions.

COG.10 Saturday, September 30th, 13:00 [Poster section: Cognitive neuroscience B]

Nature of memory engrams: conserved wiring and computational logic of cell assemblies

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There is considerable scientific interest in understanding how memory engrams are organized so that the brain can generate specific perceptions and memories. Here, we propose the Theory of Connectivity that yields the basic wiring and computational logic for organizing the microarchitecture of memory engrams that permits the emergence of knowledge and flexible behavior. This concept is based on what we term the power-of-two-based, specific-to-general permutation logic. We suggest that at the level of cell assemblies, the brain is made of functional connectivity motifs (FCMs), and each FCM is made of neural clique assemblies arranged from specific input-coding principal cell assemblies to sub-combinatorial and to general convergent input-coding cell assemblies. We propose that this wiring logic should be carried out in many brain regions regardless of anatomical variation, and should also hold true for different cognitive computing. Here, we test these predictions by using in vivo recording techniques to evaluate functional connectivity patterns of cell assemblies while animals are subjected to fearful stimuli. We show that this power-of-two-based permutation logic is widely used in cortical and subcortical circuits and is conserved for processing emotional information. Interestingly, this specific-to-general permutation logic remained largely intact although NMDA receptors — the synaptic switch for learning and memory — were deleted throughout adulthood, suggesting that the logic is developmentally pre-configured. Additionally, independent random-connectivity model analysis strongly indicate that that the specific-to-general permutation logic was constructed via the nonrandom strategy that is independent of learning in adulthood. Thus, these observations provide strong evidence that memory engrams are indeed organized via power-of-two-based permutation logic at the level of cell assemblies.

Keywords: engram, memory, assemblies

MET.01 Friday, September 29th, 13:00 [Poster section: Neuroscience methods A]

Supraspinal influence on modulation of motor evoked potentials in the leg muscles during transcutaneous electrical stimulation of the human spinal cord

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It was suggested that transcranial magnetic stimulation (TMS) and the Jendrassik maneuver can alleviate spinal motor reactions in humans. The aim of this work was to evaluate the effect of the Jendrassik maneuver and TMS on the parameters of motor evoked potentials (MEPs) of leg muscles at tSCS at Th11–Th12 vertebra level in healthy subjects. The amplitude characteristics of MEPs in m. soleus (SOL) and m. tibialis anterior (TA) were analyzed in tSCS in control and during the performance of Jendrassik maneuver in 1–10 seconds. The change in the amplitude of MEPs of these muscles was also evaluated with the combination of subthreshold TMS (90 % of TA MEPs) followed by tSCS at the conditioning-test (C-T) intervals 0–150 ms. Our results indicate that the Jendrassik maneuver within 1–10 seconds increased the reflex component (MR) of MEPs in SOL and TA totSCS. TMS facilitated MEPs of leg muscles at C-T intervals of 20 ms or more in both SOL and TA, according to the central motor conduction time for these muscles, which averaged 17 ms. In general, the effect of facilitating MEPs in the application of TMS and the Jendrassik maneuver was more obvious for SOL than for TA. This may be due to the fact that SOL is an antigravity muscle. Received results widen the range of tSCS appliance for diagnostics and rehabilitation of patients with motor disorders.

This work was funded by the Russian Science Foundation under grant 15-15-20036.

Keywords: transcutaneous electrical stimulation, transcranial magnetic stimulation, the Jendrassik maneuver, motor evoked potentials

MET.03 Friday, September 29th, 13:00 [Poster section: Neuroscience methods A]

Stability and reliability of resting heart rate variability in healthy young adults

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We assessed the time course, reliability of heart rate variability (HRV) parameters of standard RR interval recordings obtained within a single session, and to estimate the needed sample size for test-retest study protocols.

RR intervals were recorded in 50 healthy subjects during 50 minutes of rest in sitting position using Polar. Last 5 minutes of successive 10-minute long strip were analyzed for 9 HRV parameters in time domain, frequency domain and Poincare plot. Absolute reliability was assessed by standard error of measurement, relative reliability by intraclass correlation coefficient, in addition, sample size needed to detect minimal clinically important difference of ≥30 % of between-subject SD was estimated.

We found statistically significant differences in most of the HRV parameters between first 20 minutes and final 30 minutes of a session. Parameters reflecting sympathetic-parasympathetic modulation increased throughout the whole session, while parameters reflecting parasympathetic modulation decreased after 30 to 40 minutes of a session. Almost all HRV parameters had poor absolute reliability. However, most HRV parameters had good to excellent relative reliability. The estimated sample size ranged from 19–306 subjects for first 20 minutes and 36–192 subjects for final 30 minutes of a session.

We conclude that HRV is not suitable for assessing treatment or intervention effects in individual subjects, but is more appropriate for test-retest study protocols on a group of subjects. Furthermore, it seems that measurements protocols starting 20 minutes and finishing 40 minutes after assuming position are optimal for adequate stabilization and avoiding fatigue effect on HRV.

Keywords: heart rate variability, reliability

MET.02 Saturday, September 30th, 13:00 [Poster section: Neuroscience methods B]

The effects of muscle trapezius latent trigger point vibration on postural stability

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Cervical pathology is considered as one of the causes of dizziness. Our research was conducted to evaluate the effects of short-term vibration of neck latent myogenic trigger points on balance. Two groups participated in the research: 9 relevantly healthy and 32 individuals with revealed latent cervical trigger points of trapezoid muscle. Both groups were evaluated once and on equal terms. To evaluate postural balance we used posturographic approaches: Romberg test. Muscle vibration was performed once within 1 minute with a vibration frequency of 100Hz. Standard stabilography test’s results were assessed previous to muscle vibration and after it. According to Romberg rate population was ranged on 3 subgroups: within normal rates, above and below norm. It was shown that vertical posture doesn’t depend on neck myogenic trigger points. Romberg rate tended to growth if the initial point was decreased while population with the rate above the norm showed insignificant reduction up to normal. It was shown that vibration activates senso-motor integrations regardless of myogenic trigger points and as a result improves Romberg rate.

This work was funded by the subsidy allocated to Kazan Federal University for the state assignment in the sphere of scientific activities № 17.9783.2017/8.9.

Keywords: muscle vibration, myogenic trigger point, Romberg test

MOL.05 Friday, September 29th, 13:00 [Poster section: Molecular neuroscience A]

Localization of dipeptide repeat proteins and their interaction with lipid droplets in model cell lines

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Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are neurodegenerative diseases that represent two ends of a complex disease spectrum. Aggregation of RNA binding proteins is one of the hallmark pathological features of ALS/FTLD, defining them as proteinopathies. Mutations in more than 50 different genes were linked to familial ALS/FTLD, including a hexanucleotide repeat expansion in the gene C9orf72. One of the major hypotheses proposed for the pathogenicity of the expanded C9orf72 repeat mutation is the accumulation of aggregates of pathogenic dipeptide repeat (DPR) proteins: poly(GA), poly(GR), poly(PR), poly(PA), poly(GP). Several studies show that DPR proteins are neurotoxic in vitro. Lipid droplets (LDs) are dynamic structures found nearly ubiquitously in cells. Recently it has become apparent that LDs play even broader cellular roles than it was previously described. In our study, we wanted to contribute to the understanding of the potential molecular interactions between ALS/FTLD-associated proteins and cellular LDs. To this end, we prepared constructs for mammalian expression of proteins containing 125 repeats of the dipeptides GA, GP, PA, PR conjugated to eGFP and analyzed their subcellular localization after transient transfection in model cell lines by means of confocal microscopy. The hydrophobic protein poly(GA) forms distinct cytosolic aggregates in all of the model cell lines, while poly(GP) and poly(PA) appear to be evenly distributed in the nucleus and cytoplasm. Poly(PR) accumulates in nuclear aggregates. We also induced the accumulation of LDs by the addition of fatty acids in order to study the potential colocalization of DPR proteins with LDs.

Keywords: ALS, dipeptide repeat proteins, lipid droplets

MOL.11 Friday, September 29th, 13:00 [Poster section: Molecular neuroscience A]

Protein aggregation of TRIOBP-1 in patients with schizophrenia

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Schizophrenia is a devastating and chronic mental illness with a highly complex and heterogeneous genetic basis. As an alternative approach to studying its biological basis, we have been investigating the existence of specific unfolded or aggregated proteins in the brains of patients. This is partially analogous to aggregated protein deposits in neurodegenerative conditions such as Alzheimer’s disease or Parkinson’s disease.

Through purification of the insoluble protein fraction of brain samples from schizophrenia patients, and using this to immunize a mouse, we have been able to isolate a monoclonal antibody that specifically detects the insoluble protein fraction of brain samples from schizophrenia patients over an equivalent preparation derived from control individuals. This antibody was subsequently shown to have as an antigen the actin-binding protein TRIOBP-1, implying that TRIOBP-1 may exist as an insoluble or aggregated species in the brains of at least a subset of patients with a major mental illness.

Further investigation in cell lines and primary neurons has confirmed that the TRIOBP-1 protein has an intrinsic tendency to form aggregate structures when expressed in these cells and that the aggregates impact upon neurite outgrowth. Furthermore, this aggregation propensity of TRIOBP-1 is dependent on a very specific motif within the protein, currently isolated to just 9 amino acids, suggesting that a specific cellular mechanism is required for its aggregation. Through further analysis of the mechanism and consequences of TRIOBP-1 aggregation in schizophrenia, it is hoped that insight can be gained into the biological basis of this devastating psychiatric condition.

Keywords: mental illness, protein aggregation, protein misfolding, psychiatric illness, schizophrenia

MOL.13 Friday, September 29th, 13:00 [Poster section: Molecular neuroscience A]

TNIK gene and its alternative splicing regulation during neuronal differentiation

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TNIK, a genetic risk factor for schizophrenia, is a Ser/Thr kinase highly expressed in the brain and involved in synapse formation, neurogenesis and cytoskeleton dynamics. We have recently demonstrated that TDP-43, an RNA-binding protein associated with amyotrophic lateral sclerosis and frontotemporal lobar dementia, promotes the skipping of TNIK alternative exon 15, a 29 aminoacidic sequence in the intermediate region with an unknown functional role.
We further characterized TNIK exon 15 alternative splicing in different human tissues and in in vitro neuronal differentiation models, including retinoic acid-induced human neuroblastoma cells and human iPSC-derived neurons. We found that TNIKex15 mRNA isoforms were prevalent in brain, spinal cord and skeletal muscle and less expressed in liver, lung, kidney and testis. When we induced neuronal differentiation in vitro, a significant increase of TNIKex15 isoforms was observed both at transcript and protein level, while TDP-43 levels remained unchanged. Immunofluorescence analysis showed a prevalent perinuclear distribution of TNIKex15 protein in human neuron-differentiated cells compared to the other isoforms. In a minigene splicing assay, we tested whether NOVA1, a specific splicing factor in neurons, may also regulate TNIK exon15 processing. We found that NOVA1 competed with TDP-43 and completely abolished TDP-43 exon skipping activity on TNIK exon15. UV-CLIP assay confirmed a direct binding of TDP-43 and suggested an indirect effect of NOVA1 on TNIK transcript.
Our data indicate that alternative splicing of TNIK gene is tightly regulated in human brain and during neuronal development, suggesting a specific role of TNIKex15 protein isoforms in neurons which deserves further investigation.

Keywords: schizophrenia, TNIK, TDP-43, splicing

MOL.15 Friday, September 29th, 13:00 [Poster section: Molecular neuroscience A]

Proteins binding to (C4G2)n RNA repeats

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Amyotrophic lateral sclerosis and frontotemporal dementia share clinical, neuropathological and genetic features. In most cases, they develop sporadically but can also be of familial origin. The most common genetic cause of both diseases is a mutation in the gene C9orf72. The mutation is an expansion of hexanucleotide repeat – GGGGCC – in the first intron of the gene. A number of repeats in healthy individuals doesn`t exceed 23 while in disease the number of repeats is in order of hundreds to thousands. The repeats are transcribed from both sense and antisense strands and are forming G4C2 and C4G2 RNA foci in the nucleus. A proposed mechanism of action for these RNA foci is RNA toxicity by recruiting RNA binding proteins and therefore interfering with their normal cellular function. For sense foci (G4C2) n binding to paraspeckle proteins among others was shown. The aim of this work is to define RNA binding proteins that can be sequestered by antisense foci (C4G2) and determine any possible link of their sequestration with the disease process.

Keywords: ALS, FTD, C9orf72, RNA toxicity

MOL.17 Friday, September 29th, 13:00 [Poster section: Molecular neuroscience A]

I-motifs and protonated hairpins forming on the anti-sense DNA d(GGCCCC)n expansions in C9ORF72

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The intronic G4C2 hexanucleotide repeat expansion mutation in the C9ORF72 gene is the most common mutation associated with amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). The pure GC content of this mutation enables the formation of special non-B DNA structures such as G-quadruplexes and i-motifs that can act as promoters and regulatory elements affecting replication, transcription and translation of the surrounding region. C-rich sequences, similar to the anti-sense (G2C4)n strand may form i-motifs consisting of two parallel duplexes in a head to tail orientation held together by hemi-protonated C+ -C pairs under acidic conditions, however, whether such structures can form from the antisense strand under more physiological conditions remains unknown. Using CD and NMR we show for the first time that d(G2C4)n repeats do form i-motif and protonated hairpins even under near-physiological conditions. Furthermore, when both strands are present, rather than forming a DNA duplex, G-quadruplex and i-motif/hairpin structures preferentially form. This phenomenon could explain the replicational and transcriptional instability of this mutation and the i-motifs/hairpin structures could represent a novel pharmacological target for C9ORF72 associated ALS and FTLD.

MOL.02 Saturday, September 30th, 13:00 [Poster section: Molecular neuroscience B]

17β-estradiol differentially modulates ecto-5’-nucleotidase activity in the hippocampal synaptosomes of male and female rats in vitro

Natasa Mitrovic, Dunja Drakulic, Marina Zaric, Ivana Gusevac Stojanovic, Jelena Martinovic, Ivana Grkovic

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In the rodent brain, ecto-5’-nucleotidase (eN) is the main enzyme which hydrolyzes extracellular adenosine monophosphate (AMP) into adenosine. Also, it is a part of complex network influenced by ovarian steroids. To gain mechanistic insight into the role of 17β-estradiol (E2) in the modulation of eN activity, purified hippocampal synaptosomes isolated from ovariectomized female (OVX) and male rats were treated with E2 or E2-BSA (in concentration of free estradiol 10–11, 10–10, 10–9, 10–8 M) and selective agonists of ER (PPT) and ERβ (DPN) (0.1, 1, 2.5 or 5 μM). In synaptosomes obtained from OVX rats, a noticeable increase in AMP hydrolysis in full range of E2 and DPN concentrations tested (p &lt; 0.001) was demonstrated, while the rate of eN activity was not altered after incubation with PPT. E2–BSA did not change eN activity, indicating that E2 must cross the cell membrane to induce an effect on eN. The full range of E2, PPT and DPN concentrations tested induced a decrease in AMP hydrolysis (p &lt; 0.001) in synaptosomes obtained from the male hippocampus, while E2-BSA reduced AMP hydrolysis when applied in higher concentrations (10-9 M and 10-8 M of free E2). Based on the obtained results, we can conclude that E2, through activation of different estradiol receptor subtypes, exhibits the opposite effects on eN activity in male and female hippocampal synaptosomes in vitro.

Acknowledgement: Supported by Serbian Ministry of Education, Science and Technological development, project No 173044 and 41014.
Keywords: ecto-5’-nucleotidase, 17β-estradiol, estradiol receptors, hippocampus, synaptosomes

MOL.06 Saturday, September 30th, 13:00 [Poster section: Molecular neuroscience B]

Phosphorylation of FUS impairs its nucleocytoplasmic shuttling

Simona Darovic (1), Marija Srnko (1,2), Helena Motaln (1), Boris Rogelj (1,2,3)

(1) Department of Biotechnology, Jožef Stefan Institute, Ljubljana, Slovenia (2) Biomedical Research Institute BRIS, Ljubljana, Slovenia (3) Faculty of Chemistry and Chemical Technology, University of Ljubljana, Slovenia

RNA-binding proteins (RBPs) including FUS protein of the FET family are known to play a role in neurodegenerative diseases like frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS), which are characterized by progressive neuron loss. Aberrant nucleocytoplasmic localization of RNA-binding proteins, including FUS, was associated with neurotoxicity. FUS immunoreactive cytoplasmic inclusions are found in 3 % of familial ALS cases and in 10–15 % of FTLD cases. But the underlying pathological mechanisms of FUS mislocalization and aggregation in both diseases appear different. FUS is predominantly nuclear protein that possesses PY-type nuclear localization signal (NLS) at its extreme C-terminus. In ALS but not in FTLD, the mutations in the NLS of FUS are responsible for its impaired nuclear transport mediated by nuclear import receptor transportin 1 (TNPO1). We have recently reported on the phosphorylation of C-terminal tyrosine at position 526 in NLS of FUS that abolished FUS interaction with TNPO1 and potentially impaired transport of C-terminal FUS fragment into the nucleus. Since proteins with a molecular mass below 40 kDa can also passively enter/exit nucleus, here our aim was to elaborate on the phosphorylation state of Y526 in C-terminal fragment compared to full-length FUS and their exact nucleocytoplasmic localization. We show here that besides in sole C-terminal fragment of FUS, the Y526 undergoes phosphorylation also in full-length FUS in the cytoplasm. This cytoplasmic phosphorylation of Y526 may serve to fine tune the nucleocytoplasmic shuttling of FUS, to ensure that a small amount of FUS remains always present in the cytoplasm possibly for dendritic mRNA transport.

Keywords: ALS, FUS, phosphorylation, nucleocytoplasmic shuttling

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MOL.10 Saturday, September 30th, 13:00 [Poster section: Molecular neuroscience B]

Solving structures of ALS associated proteins

Vera Župunski (1), Jakob Rupert (1), Bernarda Majc (1), Urša Hribar (1), Gregor Gunčar (1), Boris Rogelj (1,2,3)

(1) Chair of Biochemistry, Faculty of Chemistry and Chemical Technology, Ljubljana, Slovenia (2) Department of Biotechnology, Jožef Stefan Institute, Ljubljana, Slovenia (3) Biomedical Research Institute, Ljubljana, Slovenia

Development of amyotrophic lateral sclerosis is underlain with different yet convergent molecular mechanisms. Cytoplasmic inclusions of otherwise predominantly nuclear protein TDP-43 is a key characteristic of the disease, leading to a loss of function of neurons. An increasing number of genetic factors have been linked to the progression, age-of-onset and susceptibility of the disease, with RNA metabolism and RNA-protein substructure being a particularly fast evolving focus of research. On the other hand, little is known about the structure of proteins of various ALS-associated genes, such as TARDBP, FUS, C9ORF72 and the recently associated ANXA11.

We have focused our research into expression and isolation of soluble proteins involved in ALS pathogenesis with the aim to solve their crystal structure. We have expressed GST- or His- tagged proteins in bacterial and mammalian expression systems using affinity and size-exclusion chromatography for isolation. Proteins predominantly sequestered in inclusion bodies, which we dissolved in urea buffer before applying to an IMAC column. On the other hand, we increased the protein solubility adding a reducing agent, glycerol and/or an increased concentration of EDTA. In order to obtain higher yield of a soluble TDP-43, the protein was co-expressed with interacting partners. Structures of proteins involved in ALS should give us an insight into interaction with known protein and RNA partners and explain physiological modifications of ALS proteins.

Keywords: ALS, TDP-43, C9orf72, protein structure

MOL.12 Saturday, September 30th, 13:00 [Poster section: Molecular neuroscience B]

Ibuprofen increased bilirubin neurotoxicity by interacting with albumin-bilirubin complex

Ane-Mary Arčan (1), Uroš Rajčević (2), Lovro Žiberna (1)

(1) Institute of Pharmacology and Experimental Toxicology, Faculty of Medicine, University of Ljubljana, Slovenia (2) Blood Transfusion Centre of Slovenia, Ljubljana, Slovenia

Aim: Bilirubin is a catabolic product of heme and is neurotoxic in high concentrations. Our aim was to study the albumin binding competition of bilirubin with the selected NSAID drugs.

Methods: We used primary neonatal rat astrocytes, mouse neuroblastoma N2A cells, and human neuroblastoma SH-SY5Y cells. We prepared two models with different bilirubin:albumin (B-A) ratios, 1:1 (400 μM bilirubin) and 1:50 (10 μM bilirubin), respectively. Then we added ibuprofen, ketoprofen, indomethacin, paracetamol and aspirin to the final concentrations of 0.1 mM and 1 mM. Cells were incubated for 24 hours, and cell viability was assessed by Alamar blue test.

Results: Bilirubin-albumin solutions (controls) decreased cell viability, while all studied drugs per se did not influence cell viability. When combined in B-A models, both ibuprofen and ketoprofen further decreased N2A and SH-SY5Y cell viability as compared to the control B-A solutions. In N2A cells, 0.1 mM ibuprofen decreased cell viability by 11% (in 1:1 B-A) and by 4% (in 1:50 B-A), and 1 mM ibuprofen decreased by 25% (in 1:1 B-A) and by 17% (in 1:50 B-A); while in SH-SY5Y cells, 1mM ibuprofen decreased cell viability by 30% (in 1:1 B-A) and by 44% (in 1:50 B-A). We observed a similar concentration-dependent decrease in cell viability in ketoprofen experiments. Other drug substances had no effect on cell viability.

Conclusions: We observed that both ibuprofen and ketoprofen decreased cell viability when combined in bilirubin-albumin solutions. We speculate that both drugs compete with bilirubin for the binding sites on albumin and that the displaced bilirubin causes increased toxicity.

Keywords: bilirubin, NSAID, albumin, cell viability

MOL.14 Saturday, September 30th, 13:00 [Poster section: Molecular neuroscience B]

Post-ischemic administration of erythropoietin: effects on the brain damage in rats exposed to focal cerebral ischemia

Jasenka Mršić-Pelčić, Kristina Pilipović, Maja Rukavina, Gordana Župan

Department of Pharmacology, Medical Faculty Rijeka, University of Rijeka, Croatia

Introduction: The purpose of our study was to investigate the influence of recombinant human erythropoietin (rhEpo) on the brain infarct volume and neuronal degeneration in the entorhinal cortex of rats exposed to the right middle cerebral artery occlusion (MCAO).

Materials and Methods: Male Hannover Wistar rats were exposed to the focal cerebral ischemia by right MCAO for 1 h. Sham operated, vehicle treated animals served as the control group. Ischemic animals received either vehicle or rhEpo (5000 IU/kg, i.p.), 3 h after induction of ischemia. Rats were sacrificed 24 h after the onset of the ischemic or sham experimental procedure. The extent of the brain infarct volume was determined by using the TTC dye at 24 h after induction of MCAO procedure in ischemic, vehicle treated animals such as in ischemic animals treated with rhEpo. Fluoro-Jade B histofluorescence was used for the evaluation of entorhinal cortical neurons undergoing neurodegenerative changes and immunohistochemical detection of NeuN for neuronal loss measurement.

Results: Our results showed that MCAO/reperfusion cause marked cortical infarction. In addition, after MCAO, prominent Fluoro-Jade B staining and the decrease in NeuN immunoreactivity were detected. Post-ischemic administration of rhEpo significantly reduced the brain infarct volume, neuronal degeneration and neuronal loss in the ischemic animals exposed to MCAO in comparison to the rats of the control group.

Conclusion: Our results suggest that post-ischemic administration of rhEpo exerts a neuroprotective potential in rats exposed to focal cerebral ischemia.

Keywords: recombinant human erythropoietin, focal cerebral ischemia, rat

MOL.16 Saturday, September 30th, 13:00 [Poster section: Molecular neuroscience B]

Comparison of small RNA expression in muscle tissue of patients with amyotrophic lateral sclerosis and healthy age-matched controls.

Anja Kovanda (1), Lea Leonardis (2), Janez Zidar (2), Blaž Koritnik (2,3), Leja Dolenc-Groselj (2), Stanka Ristić Kovačič (2), Tomaž Curk (4), Boris Rogelj (1)

(1) Department of Biotechnology, Jožef Stefan Institute, Ljubljana, Slovenia. (2) Institute of Clinical Neurophysiology, Division of Neurology, University Medical Centre Ljubljana, Slovenia. (3) Department of Neurology, Faculty of Medicine, University of Ljubljana, Slovenia. (4) Faculty of Computer and Information Science, University of Ljubljana, Slovenia

Amyotrophic lateral sclerosis (ALS) is a late onset disorder affecting upper and lower motor neurons that leads to progressive and lethal skeletal muscle atrophy. Small RNAs, including microRNAs (miRNAs) and small nucleolar RNAs (snoRNAs), act as important regulators of gene expression, both globally and in a tissue-/cell-type specific manner. In muscle, miRNAs called myomirs govern several important processes and can be dysregulated in various muscle disorders. Some of these myomirs have already shown promise for therapeutic use in cellular and animal models of ALS, however despite high evolutionary conservation of miRNAs, several differences may exist between the models and human patients, and the exact miRNA species expressed in muscle tissue of ALS patients are yet unknown. We compared the expression of small RNAs in muscle biopsies of still mobile ALS patients and healthy age-matched controls, by using Illumina small RNA sequencing and have identified differentially expressed miRNAs and snoRNAs that could serve as both biomarkers and targets for therapy development.

SYS.01 Friday, September 29th, 13:00 [Poster section: Systems neuroscience]

Influence of hypogravitation on the functional state of the myoneural synapses of rat soleus muscle

I.D. Lvova, A.O. Fedyanin, A.A. Eremeev

Kazan Federal University, Department of Human and Animal Physiology, Kazan, Russia

The aim of our study was the analysis of the functional state of the neuromuscular transmission in conditions of gravitational unloading. After 7 days of influence of microgravity, we recorded the motor (M) responses from soleus muscle induced by stimulation of the sciatic nerve with supramaximal rhythmic stimulus of 3 Hz and 50 Hz (decrement test). We estimated the amplitude of the 5th M response towards to the 1st with low-frequency stimulation (3 Hz) and the 200 M response towards to the 1st with high-frequency stimulation (50 Hz). All procedures were approved by the bioethics committee of the Kazan Federal University.

The assessment of the amplitude of the M response during stimulation with a frequency of 3 Hz did not reveal any disturbances in the synaptic transmission, the decrement of the M response from soleus muscle did not exceed 10 % and amounted to 6.6 ± 3 %. However, tetanic stimulation with a frequency of 50 Hz led to a significant depression of the induced motor potential, the decrement was 41.7 ± 6 %. Thus, the results of a high-frequency decrement test indicated sharp decreasing of the amount of acetylcholine which was available for release from the presynaptic membrane, and also decreasing of the reliability of neuromuscular transmission. The observed changes can be caused by central and peripheral mechanisms, which require further discussion.

This work was supported by RFBR, research project no. 15-04-05951a, and partially funded by the subsidy allocated to Kazan Federal University for the state assignment in the sphere of scientific activities №17.9783.2017

Keywords: gravitational unloading, rhythmic stimulus, neuromuscular transmission

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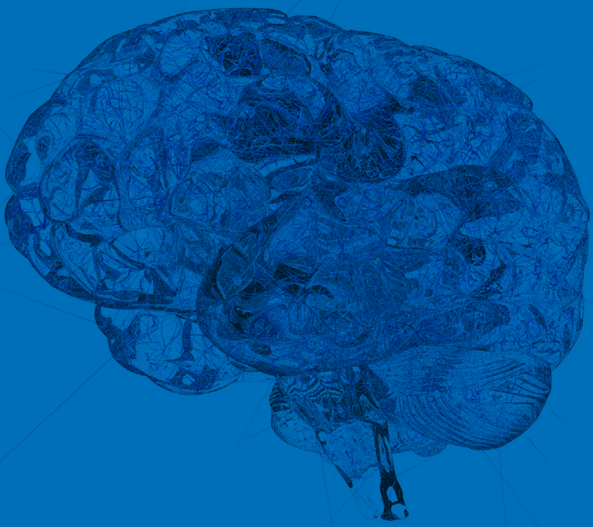

Abstracts

Educational workshop on neuroscience-based psychiatry

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www.sinapsa.org/SNC17/workshop
Faculty of Medicine, Ljubljana, Slovenia
29 September 2017

Friday, September 29th, 14:30–16:30 [Educational wokrshop on neuroscience-based psychiatry: Session I]

Borderline personality disorder

Bojana Avguštin Avčin

University Psychiatric Hospital Ljubljana

BPD is a serious mental illness marked by unstable moods, behavior, and relationships. People with a borderline level of personality organization have a fragmented sense of self and others. As a consequence they don’t have a consistent view of themselves or others, over time and across situations which results in severe and repetitive problems. The rates of co-occurring disorders, such as depression, anxiety disorders, substance abuse, along with self-harm, suicidal behaviors, and completed suicides are high. People with BPD can recover! Psychotherapy is the most important component in the treatment, leading to large reductions in symptoms that persist over time. Over the past 2 decades, many forms of psychotherapy have been developed specifically to treat the disorder.

Psychotic disorders

Borut Škodlar

University Psychiatric Hospital Ljubljana

Psychotherapy of psychotic disorders with its diverse methods and strategies can be related and mutually enriched by the neurobiological and neurocognitive findings, such as disturbances of automatic, pre-conscious processes (e.g. salience etc.) and conscious, volitional processes (e.g. executive functions, memory on different levels etc.).

Friday, September 29th, 17:00–19:00 [Educational wokrshop on neuroscience-based psychiatry: Session II]

Addiction

Mirjana Radovanovič

University Psychiatric Hospital Ljubljana

Addiction research has been at the forefront of neuroscience, which contributed evidence for many clinically well recognized phenomena, starting from the concept of addiction as a brain disease to understanding the underlying mechanisms resulting in maladaptive behavioral patterns. The presentation will focus on recent relationship and contributions of neuroscience to the state-of-the-art treatment of patients with addiction.

Psychosomatic disorders

Maja Rus Makovec

University Psychiatric Hospital Ljubljana

Somatization, the presentation of emotional distress in the form of somatic complaints, is a clinical area of huge importance in psychosomatic psychiatry. Amygdalae, paralimbic area, especially insula, are likely to play an important role. Functional somatic symptoms can be explained also by central sensitization and disrupted efferent stress pathways. Psychosomatic patients are too often labelled as treatment resistant.

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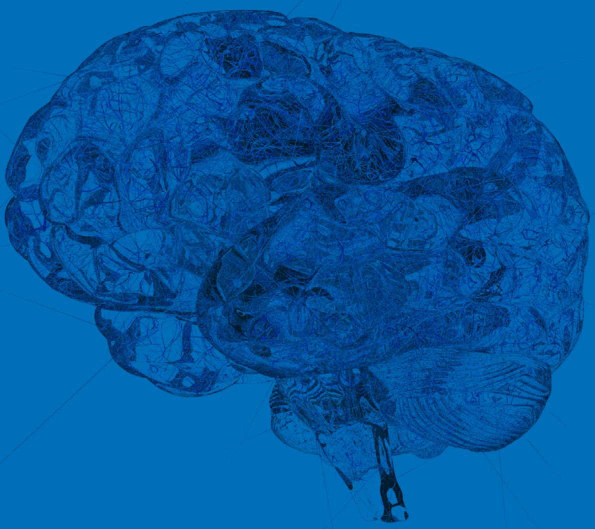

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- bolečine diabetične periferne nevropatije

Sestava Ena trda gastrorezistentna kapsula vsebuje 30 mg ali 60 mg duloksetina. **Indikacije** Zdravljenje velikih depresivnih motenj. Zdravljenje bolečine diabetične periferne nevropatije. Zdravljenje generalizirane anksiozne motnje. Zdravilo Dulsevia je namenjeno zdravljenju odraslih. **Odmerjanje in način uporabe** *Velike depresivne motnje* Začetni in priporočeni vzdrževalni odmerek je 60 mg enkrat na dan, s hrano ali brez nje. Terapevtski odziv običajno opazimo po 2 do 4 tednih zdravljenja. *Generalizirana anksiozna motnja* Priporočeni začetni odmerek je 30 mg enkrat na dan, s hrano ali brez nje. Pri bolnikih z nezadostnim odgovorom moramo odmerek povečati na 60 mg, kar je običajni vzdrževalni odmerek pri večini bolnikov. Pri bolnikih s sočasnimi velikimi depresivnimi motnjami je začetni in vzdrževalni odmerek 60 mg enkrat na dan. Bolnikom, ki se na zdravljenje s 60-miligramskim odmerkom ne odzovejo zadostno, lahko odmerek povečamo na 90 mg ali 120 mg. *Bolečina diabetične periferne nevropatije* Začetni in priporočeni vzdrževalni odmerek je 60 mg enkrat na dan, s hrano ali brez nje. Nekaterim bolnikom, ki se na zdravljenje s 60-miligramskim odmerkom ne odzovejo zadostno, lahko koristi večji odmerek, do 120 mg na dan. *Starejši* Pri starejših bolnikih prilagajanje odmerka ni potrebno, je pa pri zdravljenju potrebna previdnost. *Okvarjeno delovanje jeter* Zdravila Dulsevia ne smemo uporabljati pri bolnikih z obolenjem jeter, ki ima za posledico okvarjeno delovanje jeter. *Okvarjeno delovanje ledvic* Pri bolnikih z blago do zmerno okvarjenim delovanjem ledvic (kreatininski očistek 30–80 ml/min) *odmerka ni treba prilagajati. Zdravila* Dulsevia ne smemo uporabljati pri bolnikih z močno okvarjenim delovanjem ledvic (kreatininski očistek < 30 ml/min). *Pediatrična populacija* Varnost in učinkovitost duloksetina nista bili dokazani. Podatki niso na voljo. *Prekinitev zdravljenja* Izogibati se moramo nenadni prekinitvi zdravljenja. Ob prenehanju zdravljenja z zdravilom Dulsevia je treba odmerek zdravila v obdobju najmanj enega do dveh tednov postopoma zmanjševati, da zmanjšamo tveganje za pojav odtegnitvenih reakcij. **Kontraindikacije** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Sočasno jemanje neselektivnih ireverzibilnih zaviralcev monoaminooksidaze (MAOI). Obolenje jeter, ki ima za posledico okvarjeno delovanje jeter. Kombinacija s fluvoksaminom, ciprofloksacinom ali enoksacinom (to so močni zaviralci CYP1A2) povzroči povečane plazemske koncentracije duloksetina. Močno okvarjeno delovanje ledvic (kreatininski očistek < 30 ml/min). Uvedba zdravljenja z zdravilom Dulsevia lahko bolnike z nenadzorovano hipertenzijo izpostavi možnemu tveganju za hipertenzivno krizo. **Posebna opozorila in previdnostni ukrepi** Previdnost je potrebna pri bolnikih z manijo v anamnezi ali diagnozo bipolarne motnje in/ali epileptičnimi napadi; bolnikih z zvišanim intraokularnim tlakom ali tveganjem za akutni glavkom z zaprtim zakotjem; bolnikih, pri katerih bi zvišanje srčne frekvence ali krvnega tlaka lahko vplivalo na njihovo stanje; bolnikih, ki jemljejo zdravila proti strjevanju krvi in/ali druga zdravila, za katera je znano, da vplivajo na delovanje trombocitov (npr. nesteroidne protivnetne učinkovine ali acetilsalicilno kislino); bolnikih z znano nagnjenostjo h krvavitvam; bolnikih, ki jemljejo zdravila, ki lahko povzročijo okvaro jeter; bolnikih, ki imajo v anamnezi s samomorom povezane dogodke; bolnikih, ki pred uvedbo zdravljenja kažejo znatno stopnjo samomorilne miselnosti; bolnikih z večjim tveganjem za hiponatriemijo, kot so starejši, bolniki s cirozo, dehidrirani bolniki ali bolniki, ki jemljejo diuretike. Med zdravljenjem z duloksetinom se lahko pojavijo simptomi serotoninskega sindroma, ki lahko ogroža bolnikovo življenje, še posebej pri sočasni uporabi drugih serotoninergičnih zdravil (vključno s SSRI, SNRI, tricikličnimi antidepresivi ali triptani), zdravil, ki vplivajo na presnovo serotonina (npr. zaviralcev MAO, antipsihotikov ali drugih dopaminskih antagonistov, ki lahko vplivajo na serotoninergične nevrotransmiterske sisteme). Jemanje duloksetina so povezovali s pojavom akatizije. Simptomi se najpogosteje pojavijo v prvih nekaj tednih zdravljenja in za takšne bolnike je povečevanje odmerka lahko škodljivo. Zdravilo Dulsevia vsebuje saharozo. Bolniki z redko dedno intoleranco za fruktozo, malabsorpcijo glukoze/galaktoze ali pomanjkanjem saharoze-izomaltaze ne smejo jemati tega zdravila. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij** Zaradi nevarnosti za serotoninski sindrom duloksetina ne smemo uporabljati v kombinaciji z MAOI ali v 14 dneh po prenehanju zdravljenja z MAOI. Sočasno uporabo zdravila Dulsevia s selektivnimi reverzibilnimi MAOI (npr. z moklobemidom) odsvetujemo. Antibiotik linezolid je reverzibilen, neselektiven MAOI in ga bolniki, ki se zdravijo z zdravilom Dulsevia, ne smejo jemati. Zdravila Dulsevia ne smemo dajati skupaj z močnimi zaviralci CYP1A2 (npr. s fluvoksaminom). Pri jemanju zdravila Dulsevia v kombinaciji z drugimi centralno delujočimi zdravili ali snovmi, vključno z alkoholom in pomirjevali, je potrebna previdnost. Previdnost svetujemo tudi, če zdravilo Dulsevia dajemo sočasno z zdravili, ki jih presnavlja predvsem CYP2D6 (npr. z risperidonom, tricikličnimi antidepresivi), zlasti če imajo ozek terapevtski indeks (npr. flekainid, propafenon, metoprolol). Zaradi možnega povečanega tveganja za krvavitev je potrebna previdnost pri kombinaciji duloksetina in peroralnih antikoagulantov ali antitrombotičnih zdravil. Pri kadilcih so plazemske koncentracije duloksetina skoraj za 50 % manjše kot pri nekadilcih. **Plodnost, nosečnost in dojenje** Ustreznih podatkov o uporabi duloksetina pri nosečnicah ni. Zdravilo Dulsevia naj se v nosečnosti uporablja le, če možna korist upravičuje možno tveganje za plod. Ženskam je treba svetovati, naj obvestijo zdravnika, če med zdravljenjem zanosijo ali če načrtujejo nosečnost. Ker varnost uporabe duloksetina pri dojenčkih ni znana, uporabo zdravila Dulsevia med dojenjem odsvetujemo. **Vpliv na sposobnost vožnje in upravljanja s stroji** Jemanje zdravila Dulsevia lahko povzroča sedacijo in omotico. **Neželeni učinki** Najpogosteje so poročali o neželenih učinkih, kot so slabost, glavobol, suha usta, zaspanost in omotica. Večina pogostih neželenih učinkov je bila blaga do zmerna, običajno so se pojavili kmalu po uvedbi zdravila, večina jih je izginila že med nadaljevanjem zdravljenja. Pogosto so bili opaženi zmanjšanje apetita, nespečnost, agitacija, zmanjšanje libida, anksioznost, nenormalen orgazem, nenavadne sanje, letargija, tremor, parestezija, zamegljen vid, tinitus, palpitacije, zvišan krvni tlak, rdečica, zehanje, zaprtje, driska, bolečina v trebuhu, bruhanje, dispepsija, napenjanje, povečano znojenje, izpuščaj, mišično-skeletna bolečina, mišični krč, dizurija, polakizurija, erektilna disfunkcija, motnje ejakulacije, zapoznela ejakulacija, padci, utrujenost, zmanjšanje telesne mase. Ostali neželeni učinki se pojavijo občasno, redko ali zelo redko. **Imetnik dovoljenja za promet z zdravili** Krka, d. d., Šmarješka cesta 6, 8501 Novo mesto, Slovenija. **Način izdajanja zdravila** Samo na zdravniški recept. **Oprema** 28 trdih gastrorezistentnih kapsul po 30 mg in 60 mg duloksetina. **Datum zadnje revizije besedila** 18. 11. 2015.

9/2017, 2017-32661, Slovenija, MK/KS.

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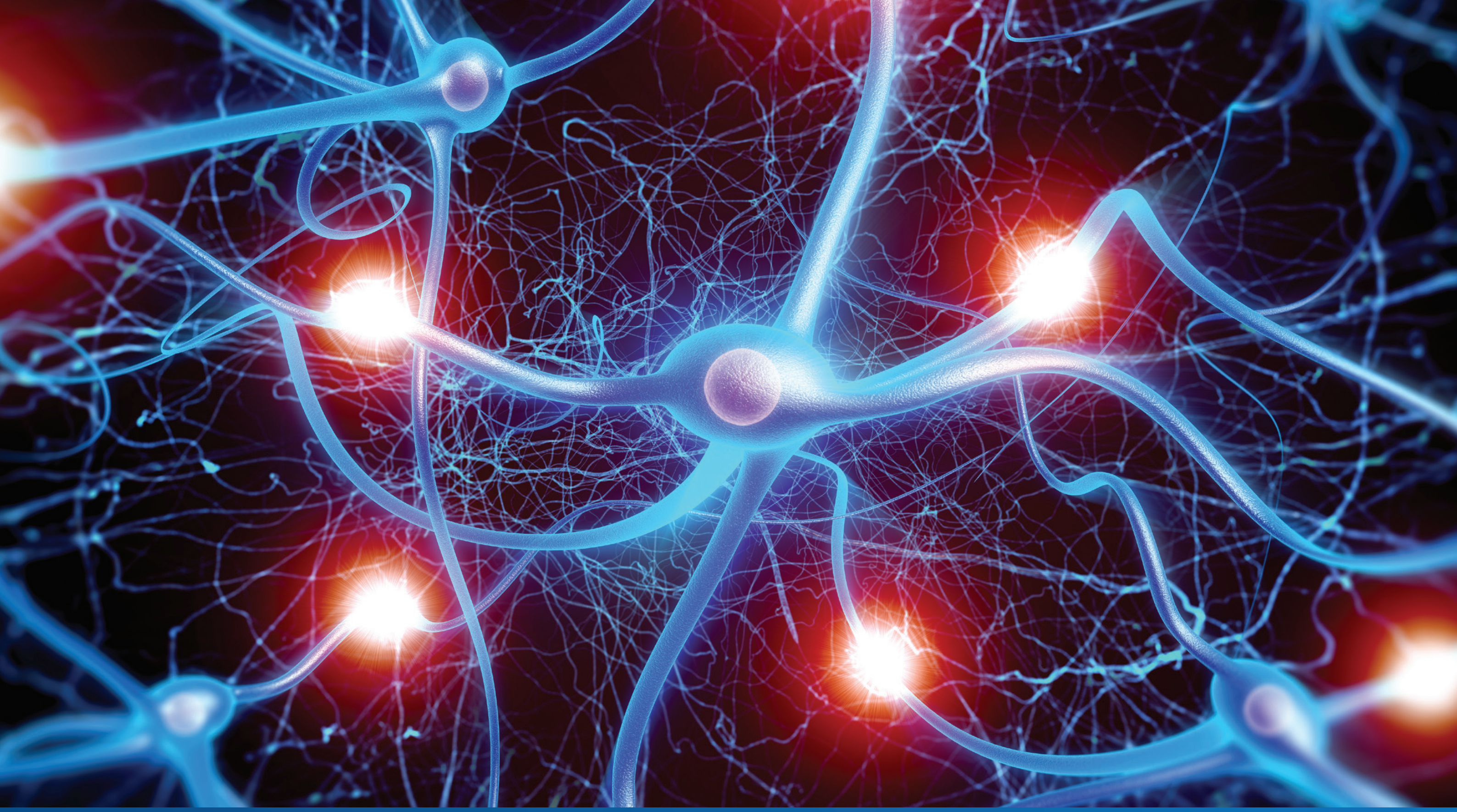

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Janssen R&D

"Our goal is to drive the types of discoveries that will ultimately change the lives of patients by transforming the way neuropsychiatric diseases and pain conditions are managed."

David Bredt,
Global Head of Discovery, Janssen R&D

Advancing new science

- Transforming care for treatment resistant depression
- Leading the movement to non-opioid era
- Advancing schizophrenia with freedom from frequent administration, long-term effectiveness, convenience, allowing to focus on holistic care
- Broad programme in Alzheimer's with focus on disease interception
- Developing diagnostics and biomarkers to bring forth predictive tools and pre-emptive, precision medicines

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