

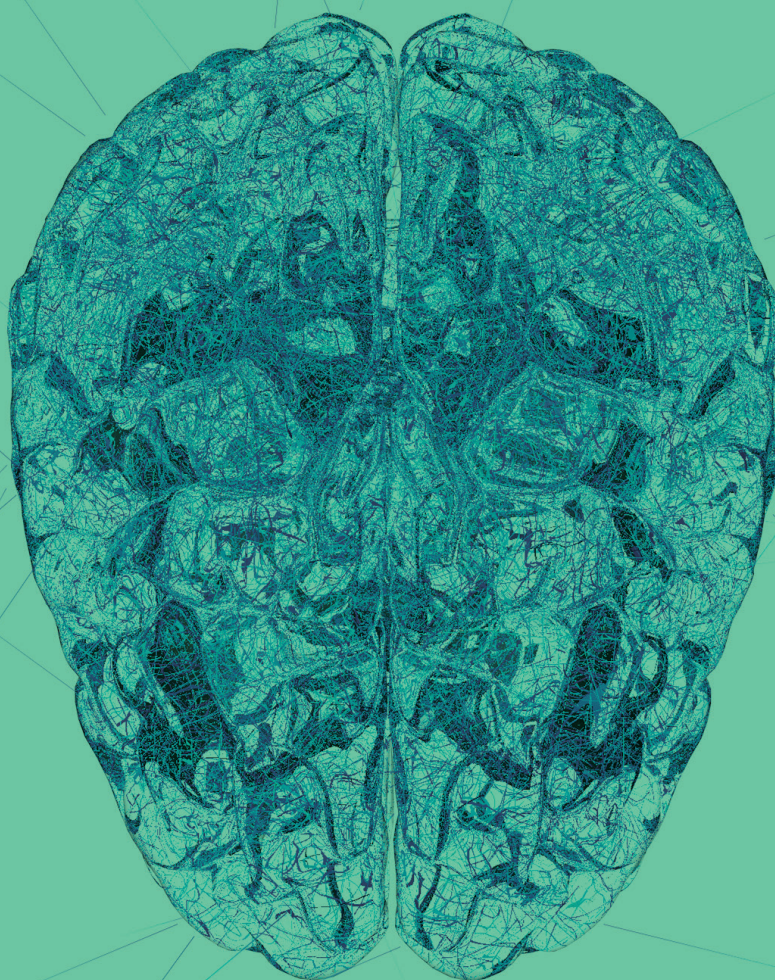


SiNAPSA

SLOVENSKO DRUŠTVO ZA NEVROZNANOST
SLOVENIAN NEUROSCIENCE ASSOCIATION

SNC'21

SINAPSA NEUROSCIENCE CONFERENCE '21



23-25 September, 2021
LJUBLJANA, SLOVENIA

Sinapsa Neuroscience Conference '21

Ljubljana, 23–25 September 2021

Organised by

SiNAPSA, Slovenian Neuroscience Association

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Maja Bresjanac (Chair), Lana Blinc, Matjaž Deželak, Blaž Koritnik, Matej Perovnik, Viktorija Radotič

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Editors

Andraž Matkovič, Maja Bresjanac

Design

Klemen Trupej, Damjan Osredkar, Grega Repovš

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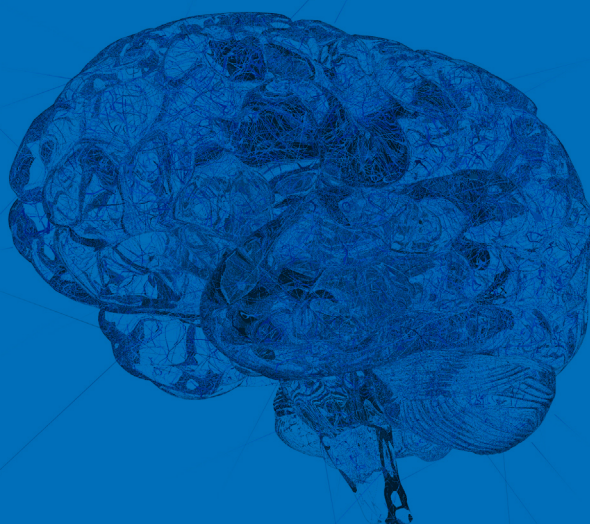


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BOOK OF ABSTRACTS

www.sinapsa.org/SNC21
Ljubljana, Slovenia
23–25 September 2021

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Programme at a glance

	Thursday, September 23	Friday, September 24	Saturday, September 25
9:00			
10:00			
11:00		11:00–12:00 Biogen & Pfizer Satellite symposium	11:00–12:00 Poster session I
12:00		12:00–12:45 Dr. Janez Faganel Memorial lecture: Giuseppe Lauria	12:00–12:45 Plenary talk: Eiko Fried
13:00	13:45–14:00 SNC'21 Opening	13:00–18:00 Ljubljana Clinical Neurophysiology Symposium	13:00–14:30 Symposium II: Deep Brain Stimulation for Movement Disorders
14:00	14:00–16:00 Hot topic: SARS-CoV-2 and Brain		13:00–15:00 Symposium III: Music and Brain - Evidence Based Music Interventions in Medicine
15:00			15:00–15:45 EWPM I: Proteostasis & PM Disease
16:00	16:00–18:00 Symposium I: Metabolic Brain Imaging in Neurodegenerative Disorders		15:00–17:00 Symposium IV: Brain Health Across the Lifespan - Findings from the Lifebrain Project
17:00			15:45–17:45 EWPM II: Tauopathies, a-synucleinopathies, poly-Q, TDP43
18:00	18:15–19:00 Plenary talk: Thilo van Eimeren	18:00–18:30 Roche Satellite symposium	17:00–17:45 Plenary talk: Tracy Bale
19:00			17:45–18:00 SNC'21 Closing
20:00			
21:00			

EWPM - Educational workshop on CNS protein misfolding

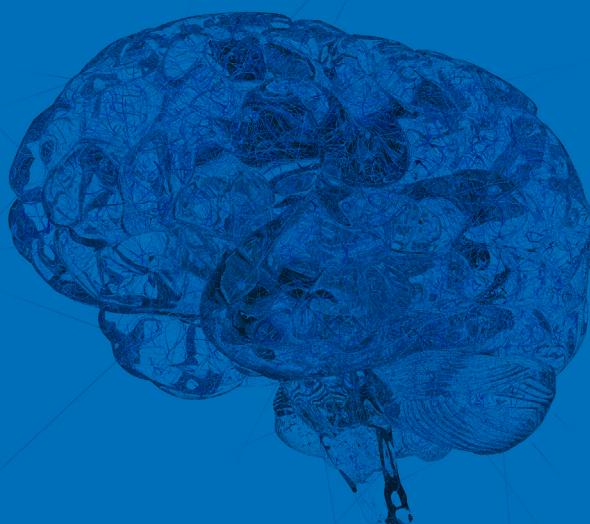


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SiNAPSA Neuroscience Conference '21 Programme

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Ljubljana, Slovenia
23–25 September 2021

SiNAPSA Neuroscience Conference '21 Programme

Thursday, 23 September

13:45—14:00 **Opening of the SNC'21**

14:00—16:00 Symposium
SARS-CoV-2 and Brain
Chairs: Maja Bresjanac

Neuro-COVID - what it is and what it is not
Raimund Helbok

Neurological Associations of COVID-19 Vaccines
Jennifer Frontera

Learning during the pandemic: mapping potential educational inequalities across Europe
Zsuzsa Blaskó

Cognitive and Neurological Consequences of COVID-19
Adrian Owen

16:00—18:00 Symposium
Metabolic Brain Imaging in Neurodegenerative Disorders
Chair: Matej Perovnik and Maja Trošt

Mechanisms of tau pathology spreading in Alzheimer's disease and 4R tauopathies
Nicolai Franzmeier

Developing and Interpreting a Deep Learning Model for Alzheimer's Disease Tracking
Alison Deatsch

Technical Factors Affecting Image Quality in PET
Mauro Namías

Cognition-related functional topographies in Parkinson's disease: Localized loss of the ventral default mode network
Katharina A Schindlbeck

Metabolic correlates in PSP clinical subtypes
Gloria Martí-Andrés

Specific Metabolic Brain Patterns in Alzheimer's dementia and dementia with Lewy bodies
Matej Perovnik

Correlations between brain metabolism and neuropathology in sporadic Creutzfeldt-Jakob disease
Tomaž Rus

18:15—19:00 Plenary talk
Can brain imaging unravel the tangled web of neurodegeneration?
Thilo van Eimeren

Friday, 24 September

11:00—12:00 **Short Oral Presentations Session I**

12:00—12:45 Dr. Janez Faganel Memorial lecture
Small fiber neuropathy
Giuseppe Lauria

13:00—14:30 Symposium
Deep Brain Stimulation for movement disorders – A neuroimaging perspective
Chair: Maja Trošt and Dejan Georgiev

Non-motor symptoms in Parkinson's disease and Dystonia: Neuroimaging perspective
Vladimira Vuletić

The effect of Deep Brain Stimulation on Brain Metabolism in Movement Disorders
Maja Trošt

Parkinson's disease as a network disorder: Lessons from connectivity studies
Rok Berlot

Frequency modulation in deep brain stimulation: Does it work and is there neuroimaging proof of its action?
Dejan Georgiev

Impulsivity in STN-DBS PD: More than a unitary phenomenon
Tjaša Mlinarič

Effects of subthalamic nucleus deep brain stimulation on language in advanced Parkinson's disease
Živa Drakulić

15:00—19:45 Workshop
Educational Workshop on Proteostasis and Protein Misfolding in CNS Disorders

19:00—19:45 AOŽ Memorial lecture
Genetic prion disorders and patient-scientist's mandate
Sonia M. Vallabh

19:45—20:30 **Neuroscience and Society Dialogue: Conversation with Dr. Sonia M. Vallabh**

Saturday, 25 September

11:00—12:00 **Short Oral Presentations Session II**

12:00—12:45 Plenary talk

Systems all the way down: studying mental health problems as biopsychosocial systems

Eiko Fried

13:00—15:00 Symposium

Music and Brain: Evidence-based music interventions in medicine

Chair: Igor M. Ravnik and Uroš Kovačič

Neurology of Music and Brain

Daniele Schoen

Research towards evidence-based music interventions

Stefan Koelsch

The mother's voice, singing and speaking, as a special tool for early interventions in the NICU

Manuela Filippa

Heart rate variability in relation to self-selected music or music genres preselected by the researchers

Uroš Kovačič

15:00—17:00 Symposium

Brain health across the lifespan – Findings from the Lifebrain project

Chair: Isabelle Budin-Ljøsne

Ageing and brain imaging in Lifebrain

Klaus P. Ebmeier for Lifebrain Consortium

What can blood biomarkers tell us about the brain?

Christian A. Drevon

What is brain health? Perceptions of respondents to the Global Brain Health Survey

Isabelle Budin-Ljøsne for Lifebrain Consortium

Brain asymmetry in aging and Alzheimer's disease

James M. Roe

17:00—17:45 Plenary talk

Extracellular vesicles as stress signals: Identifying novel mechanisms of neurodevelopmental programming

Tracy Bale

17:45—18:00 **SNC'21 Closing**

Poster sessions

Friday, 24 September

11:00—12:00 **Short Oral Presentations Session I**

Effect of repetitive transcranial magnetic stimulation on language performance in Alzheimer's Disease: a Slovene-speaker case study

Georgia Roumpea

The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog): standardisation of Slovenian version

Janina Ulbl

DNA methylation of candidate genes BDNF and COMT in Alzheimer's disease

Alja Videtić Paska

Expression of Na⁺,K⁺-ATPase isoenzymes and myokines in cultured human myotubes innervated by rat spinal cord explants

Vid Jan

Saturday, 25 September

11:00—12:00 **Short Oral Presentations Session II**

Role of PDGFR α - Integrin interactions in Anoikis resistance mediated glioblastoma progression

Pampa Pain

HMGB1 inhibition attenuates lipopolysaccharide (LPS)-induced neuroinflammation, cognitive dysfunction and sickness behavior

Devlina Ghosh

Educated vs. lay public view of neuroscience and science based brain health recommendations in Slovenia

Matej Perovnik

Physicians' standpoints for the use of music-based interventions in Slovenian health care system

Ana Kuder

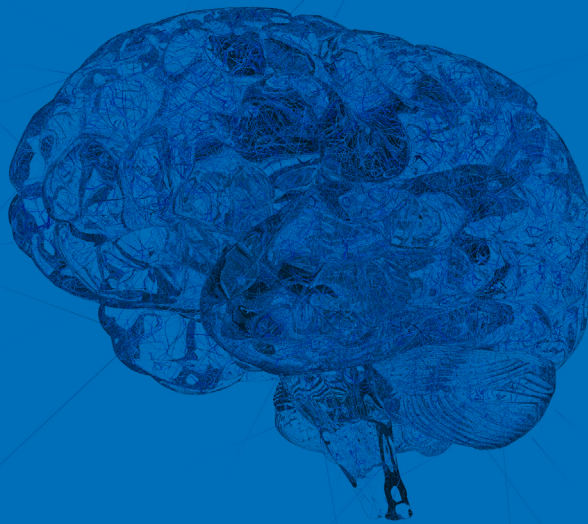


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Educational workshop on CNS protein misfolding

www.sinapsa.org/SNC21/workshop
Ljubljana, Slovenia
24 September 2021

Friday, 24 September

- 15:00—15:45 **Proteostasis Collapse: A Basis for Aging and Neurodegenerative Diseases**
Richard I. Morimoto
- 15:45—16:15 **An update on Tau-related diseases**
Gabor G. Kovacs
- 16:15—16:45 **TDP-43 proteinopathies**
Boris Rogelj
- 16:45—17:15 **Now it is time for research to crack Parkinson's disease**
Patrik Brundin
- 17:15—17:45 **Huntington's disease**
Roger A. Barker
- 17:45—18:15 **Transmissible Spongiform Encephalopathies**
Adriano Aguzzi
- 18:15—18:45 **A structural biologist's view of neuroscience**
Holger Wille
- 19:00—19:45 **Genetic prion disorders and patient-scientist's mandate**
Sonia M. Vallabh

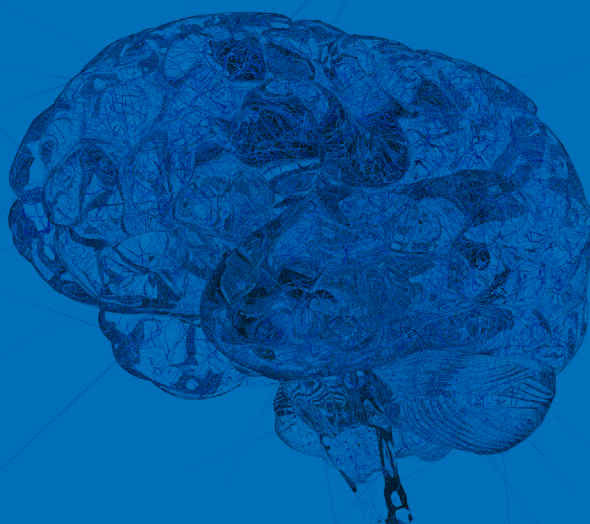


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Clinical Neurophysiology Symposium

www.sinapsa.org/SNC21/simpozij

Ljubljana, Slovenia

24 September 2021

Friday, 24 September

- 11:00—11:30 **Biogen satellite symposium: Nusinersen treatment of spinal muscular atrophy**
Vladka Salapura
- 11:30—12:00 **Pfizer satellite symposium: From transthyretin neuropathy to cardiomyopathy**
Janez Zidar, Gregor Zemljič
- 12:00—12:45 Dr. Janez Faganel Memorial lecture
Small fiber neuropathy
Giuseppe Lauria
- 13:00—18:00 Symposium
Ljubljana Clinical Neurophysiology Symposium
Chair: Blaž Koritnik
- Pattern recognition approach to neuropathy and neuronopathy**
Richard J. Barohn
- New 2021 EAN/PNS CIDP guideline**
Peter Van den Bergh
- Multifocal motor neuropathy**
Bruce V. Taylor
- Paraproteinemic neuropathies**
Elie Naddaf
- Inherited neuropathies**
Michaela Auer-Grumbach
- Small fiber neuropathy – Slovenian experience**
Mateja Baruca Grad
- Measurement of axonal excitability**
Mihai Moldovan
- Investigations of cardiovascular autonomic nervous system**
Ellen Merete Hagen
- Utility of ultrasonography in polyneuropathies**
Simon Podnar
- 18:00—18:45 **Roche satellite symposium: SMA - new treatment options**
Damjan Osredkar, Lea Leonardis

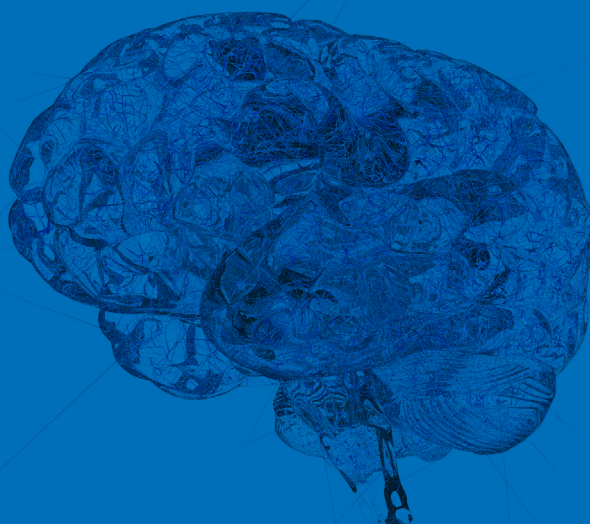


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Abstracts

SNC'21 Plenary and Special Lectures

www.sinapsa.org/SNC21

Ljubljana, Slovenia

23–25 September 2021

Thursday, September 23rd, 18:15

Can brain imaging unravel the tangled web of neurodegeneration?

Thilo van Eimeren, MD

University Hospital Cologne, Multimodal Neuroimaging Group, Department of Nuclear Medicine, Cologne & Department of Neurology, University Hospital Cologne, Cologne & German Center of Neurodegenerative Disease (DZNE), Cologne, Germany

Many generations after James Parkinson, Friedrich Lewy, Arnold Pick and Alois Alzheimer, neuroscientists are still facing a mystery about the origins and mechanisms of neurodegenerative diseases. Every new generation holds even more sophisticated scientific tools in their hands to chop away some parts of the obscurity enclosing this enigma. The investigation of histopathology and the identification of certain proteinaceous formations have paved the way to a deeper understanding of neurodegenerative processes. Yet, investigating the brain under the microscope after death is like seeing a still frame of the end of a movie. In order to unveil the dynamic transformations leading up to protein pathologies, we would want to see “the whole movie”. Brain imaging, including PET imaging of molecular targets, is the ultimate and unique tool to investigate, track, and map metabolic, functional, molecular and structural changes over the course of disease development. A dynamic development that seems to start at a cross-road between various internal biological factors, live style decisions and the exposition to external influences.

Brain imaging increasingly provides profound and novel insights in these dynamic processes from molecular changes to system failure. Cumulative evidence points to a triad of vulnerability, comprising the specific strain of misfolded protein, local cellular properties, and the way brain areas are functionally and structurally connected (‘connectomics’). We may now, for the first time, truly be able to untangle the web of neurodegenerative diseases and ultimately trace the pathways back to their origins.

Friday, September 24th, 12:00

Small fiber neuropathy

Giuseppe Lauria, MD

Università di Milano - Fondazione I.R.C.C.S., Istituto Neurologico Carlo Besta · Clinical Neurosciences Milan, Italy

In the last five years, knowledge on small fibre neuropathy has been widened by new preclinical and clinical leading to a more comprehensive approach to patients in clinical practice and research. The spectrum of clinical features has been widened from the classical presentation of burning feet as length-dependent small fibre neuropathy to that of small fibre dysfunction and/or degeneration associated with focal, diffuse and episodic neuropathic pain syndromes. The involvement of small nerve fibres in neurodegenerative diseases has been further defined, challenging the relationship between neuropathic pain symptoms and small fibre loss.

The clinical reliability of skin biopsy has been strengthened by the availability of normative values for both the immunohistochemistry techniques used and their comparison, and by side and short-term follow-up analyses. New studies expanded the panel on genes involved in small fibre neuropathy and opened new avenues for personalised therapies.

Friday, September 24th, 15:00

Proteostasis Collapse: A Basis for Aging and Neurodegenerative Diseases

Richard I. Morimoto, PhD

Bill and Gayle Cook Professor of Biology, Rice Institute of Biomedical Research, Northwestern University Evanston, IL 60201

Aging is associated with the programmed decline of cell protective stress responses and the loss of cellular proteostasis essential to prevent the accumulation of misfolded and aggregated proteins common to all neurodegenerative diseases. We have employed multiple biological systems and approaches to identify the composition of the proteostasis network (PN) that regulates protein synthesis, folding, translocation and degradation, to demonstrate how the PN determines the stability and function of the proteome in health and fails in aging and diseases, and genetic and small molecule approaches to reset the PN and suppress aggregation and amyloid formation.

Our current efforts are to identify the earliest events that predict proteostasis failure in neurons and other tissues.

Saturday, September 25th, 12:00

Systems all the way down: studying mental health problems as biopsychosocial systems

Eiko Fried, PhD

Associate Professor at Leiden University, The Netherlands

We're not doing so well in mental health research. Despite global research efforts and increasing political and funding priorities, our understanding of mental health problems, and our ability to treat them, remain disappointing. In this talk, I sketch three reasons for the lack of progress. The first is diagnostic literalism: we may be looking at the wrong phenotypes. The second is reductionism: unreasonable simplifications—ranging from the Freudian unconscious to the idea that mental illness can be fully understood by investigating the brain—hinder progress. The third barrier is lack of theory building and testing: research efforts are largely exploratory, and few overarching, formal theories or models exist. I will suggest that conceptualizing and studying mental health problems as complex, biopsychosocial systems offers unique opportunities, and conclude by reviewing current efforts to do so.

Saturday, September 25th, 17:00

Extracellular vesicles as stress signals: Identifying novel mechanisms of neurodevelopmental programming

Tracy Bale

Center for Epigenetic Research in Child Health & Brain Development, University of Maryland School of Medicine, Baltimore, MD, USA

Extracellular vesicles (EVs) are a novel signaling mechanism involved in numerous developmental processes including the transmission of parental life experiences across generations. The protein and sncRNA content of EVs is dramatically altered by stress in mice and trauma in humans, and these changes can impact the course and rate of embryo and fetal brain development, altering adult brain function.

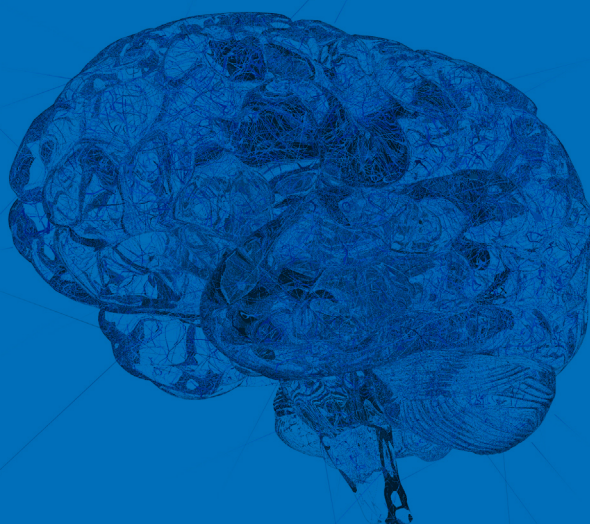


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Abstracts

SNC'21 Thematic Symposia

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Thursday, September 23rd, 14:00 [Symposium: SARS-CoV-2 and Brain]

Neuro-COVID - what it is and what it is not

Raimund Helbok**Medical University of Innsbruck, Department of Neurology, Neurocritical Care Unit, Anichstr.35, 6020 Innsbruck, Austria, Europe**

Since the recognition of SARS-CoV-2 outbreak in 2019, several neurological manifestations have been reported. Prevalence rates largely vary (6-84%) and range from mild (headache, hyposmia, myalgia) to severe (encephalopathy, strokes, seizures). Recently, "Long-COVID" has been recognized as novel entity and long-term neurological consequences or novel manifestations after COVID-19 have been reported.

This talk will cover pathophysiologic aspects of "Neuro-COVID" clinical course and longterm outcomes.

Thursday, September 23rd, 14:00 [Symposium: SARS-CoV-2 and Brain]

Neurological Associations of COVID-19 Vaccines

Jennifer Frontera**NYU Langone Health, NY, USA**

Despite widespread availability of extremely effective SARS-CoV-2 vaccines in the U.S., hesitancy related to concerns over vaccine safety have hampered efforts to quell the COVID-19 outbreak, leading to a pandemic of the unvaccinated. Vaccine safety data as reported by drug companies, the FDA and the CDC illuminate the safety of the vaccine, particularly compared to the high risks of morbidity and mortality related to COVID-19 illness itself. However, incidence rates of neurological complications from SARS-CoV-2 vaccinations have not been reported. The CDC Vaccine Adverse Event Reporting System (VAERS) contains clinician and patient self-reported complications of a variety of vaccines available in the U.S. including Pfizer, Moderna, and J & J SARS-CoV-2 vaccines.

In this talk, we explore the incidence of neurological adverse events following SARS-CoV-2 vaccination.

Thursday, September 23rd, 14:00 [Symposium: SARS-CoV-2 and Brain]

Learning during the pandemic: mapping potential educational inequalities across Europe

Zsuzsa Blaskó**Joint Research Centre, European Commission**

Since the beginning of the Covid-19 pandemic there has been little doubt that physical school closures would lead to a substantial learning loss among school children. It was also clear that the size of this loss will vary across student groups, with the most vulnerable ones falling further behind. These predictions followed from our pre-existing knowledge on how (other types of) disruptions of education can affect learning progress. Over a year after the pandemic started we still have only limited evidence on the actual learning consequences of the school closures. The evidence we have however is very worrying, as it seems to fully justify early concerns. In my presentation I will give an overview of existing research on the size of the Covid-19 related learning losses in Europe and the socioeconomic differences in it. Relying on our research study I will show how (in a situation of severe data-lack) pre-Covid educational data can help to assess the relative size of learning losses and the related social inequalities across the various countries of Europe. Our analyses help to identify countries with the biggest risk of experiencing an educational crisis due to the pandemic and call for interventions to mitigate the damage.

You can download the full paper here: <https://www.iza.org/publications/dp/14298/learning-loss-and-educational-inequalities-in-europe-mapping-the-potential-consequences-of-the-covid-19-crisis>

Thursday, September 23rd, 14:00 [Symposium: SARS-CoV-2 and Brain]

Cognitive and Neurological Consequences of COVID-19

Adrian Owen

There are now more than 160 million people in the world with COVID-19 and 1.3 million in Canada alone. As people recover, more and more are reporting cognitive challenges like problems with memory, concentrating and problem solving. These problems could be caused by many aspects of COVID-19 - from direct viral effects on the brain itself, to indirect effects due to inflammation, blood clots, low oxygen levels, sedation and spending time on a ventilator. In June 2020, we launched a global, online longitudinal study of the short and long-term cognitive sequelae of COVID-19 infection (covidbrainstudy.com).

In this talk, I will present the first results from this study, which address the following questions:

- i) If COVID-19 infection does result in significant cognitive impairment, what cognitive domains are specifically affected?
- ii) Is the burden of cognitive impairment greater in those with more severe infection (i.e., those who require ICU stay or hospitalisation outside the ICU)
- iii) Are there interactions with sex, age and medical risk factors that result in greater impact in some populations?

Thursday, September 23rd, 16:00 [Symposium: Metabolic Brain Imaging in Neurodegenerative Disorders]

Mechanisms of tau pathology spreading in Alzheimer's disease and 4R tauopathies

Nicolai Franzmeier

Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig-Maximilians-Universität LMU, Munich, Germany

The progressive spread of tau pathology throughout the brain is a key driver of neurodegeneration and cognitive decline across a variety of neurodegenerative diseases including Alzheimer's disease (AD) and 4-repeat (4R) tauopathies. Thus, understanding tau spreading mechanisms may be critical in order to develop tau targeting interventions. Pre-clinical studies have emphasized that tau spreads across inter-connected neurons in an activity-dependent manner, suggesting that tau spreading is an active process routed by the brains' connectome. Thus, we aimed to translate this concept of connectivity-mediated tau spreading to AD and 4R tauopathy patient data. To this end, we combine tau-PET imaging (i.e. Flortaucipir tau-PET in AD vs. PI2620 tau-PET in 4R tauopathies) and regional post-mortem tau-assessments (in 4R tauopathies) with resting-state functional MRI-based connectivity data. Across both AD and 4R tauopathies, we observe that i) functionally connected brain regions show correlated tau-PET levels and that ii) tau-PET deposition patterns follow the seed-based connectivity pattern of regions with earliest tau pathology (i.e. tau epicenters). A congruent result pattern can be detected using post-mortem tau data in 4R tauopathy patients, where functionally connected brain regions show correlated post-mortem tau levels. Using longitudinal tau-PET data in AD patients, we show further that tau spreads successively from circumscribed tau epicenters across closely connected brain regions, which can be used for patient-centered prediction of future tau spreading. Together, our findings support a close link between functional brain networks and tau spreading in AD and 4R tauopathies, supporting the concept of connectivity-mediated tau spreading in neurodegenerative tauopathies.

Thursday, September 23rd, 16:00 [Symposium: Metabolic Brain Imaging in Neurodegenerative Disorders]

Developing and Interpreting a Deep Learning Model for Alzheimer's Disease Tracking

Alison Deatsch(1), Matej Perovnik(2,3), Robert Jeraj(1,3)

1 University of Wisconsin – Madison, Madison, WI

2 University Medical Centre Ljubljana, Ljubljana, Slovenia

3 University of Ljubljana, Ljubljana, Slovenia

Despite a clear clinical need, there is a lack of a comprehensive, generalizable tool for reliable diagnosis of Alzheimer's disease (AD). Significant work has been done to develop deep learning networks for

this purpose. However, models employing 18F FDG PET images and longitudinal data are underdeveloped, despite potential advantages in performance improvement and early detection. Our goal is to develop a deep learning model to distinguish brain images of patients with AD from normal controls, and to interpret this model by (1) examining the influence of longitudinal data, disease duration, and imaging modality on performance and (2) identifying regions of the brain which are most influential to the network's decision.

We develop a convolutional neural network (CNN) with a cascaded recurrent neural network (RNN) for binary classification. Attention heatmaps are output to visualize the CNN decision-making. Two sets of brain images and clinical data from ADNI were used for training and testing: (1) 560 FDG PET scans from 422 patients, of which 122 have multiple timepoints with 1-2 year gaps, (2) 418 T1-weighted MRI from 193 patients, of which 130 have multiple timepoints. We validate the model with an independent dataset of 104 FDG PET scans. ROC analysis revealed a maximum area under the curve (AUC) of 0.87 ± 0.06 . Model comparison showed that adding longitudinal information improves classification performance over single timepoint analysis and that the PET-trained network outperforms MRI. CNN heatmaps illuminate imaging patterns indicative of AD and move this work toward identification of a quantitative imaging biomarker for AD diagnosis.

Thursday, September 23rd, 16:00 [Symposium: Metabolic Brain Imaging in Neurodegenerative Disorders]

Technical Factors Affecting Image Quality in PET

Mauro Namías(1) and Robert Jeraj(2,3)

1: Medical physics department, Fundación Centro Diagnóstico Nuclear, Buenos Aires, Argentina

2: Department of Medical Physics, University of Wisconsin – Madison, United States of America

3: Faculty of Mathematics and Physics, University of Ljubljana, Ljubljana, Slovenia

Image quality, quantitative accuracy and reproducibility in PET imaging can be affected by different factors, such as scanner design, acquisition protocols and reconstruction settings, among others. Spatial resolution can be modeled by the modulation transfer function (MTF) of the system, while noise can be modeled by the noise power spectrum (NPS). We present an image formation model based on the MTF and the NPS of the reconstructed images, which includes a correlated and signal-dependent noise term. A simplified and automated methodology to estimate the MTF and NPS from cylindrical phantom scans is presented, based on previously developed quantitative harmonization techniques. The MTF is estimated from the edges of the cylindrical phantom, while the NPS is estimated from uniform regions inside it. In addition, a framework to simulate realistic images for complex objects like the brain, based on the resolution and noise measurements, is also presented. The concepts of signal to noise ratio and noise equivalent quanta will be introduced as tools to model signal detectability by an ideal observer. The impact of different reconstruction settings (voxel size, iterations, filters, etc.) and acquisition times will be presented and we will briefly discuss optimization strategies to improve image quality.

Thursday, September 23rd, 16:00 [Symposium: Metabolic Brain Imaging in Neurodegenerative Disorders]

Cognition-related functional topographies in Parkinson's disease: Localized loss of the ventral default mode network

Katharina A Schindlbeck(1), An Vo(1), Paul J Mattis(1,2), Kersten Villringer(3), Frank Marzink(4), Jochen B Fiebach(3), and David Eidelberg(1)

1 Center for Neurosciences, The Feinstein Institutes for Medical Research, Manhasset, NY

2 Department of Neurology, Northwell Health, Manhasset, NY

3 Center for Stroke Research, Charité – Universitätsmedizin Berlin, Hindenburgdamm 30, 12200 Berlin, Germany

4 Department of Neurology, Charité – Universitätsmedizin Berlin, Hindenburgdamm 30, 12200 Berlin, Germany

Background

Cognitive decline, a common symptom in patients with Parkinson's disease (PD), has been associated with stereotyped changes in normal resting state networks and cognition related networks evolving over time. We sought to determine whether functional network abnormalities seen in patients with Parkinson's disease (PD) and cognitive decline reflect the loss of the default mode network (DMN), the gain of an abnormal network topography, or a combination of both.

Methods

We first analyzed 18F-FDG PET metabolic images to evaluate network expression levels in a large PD sample (n=153) with varying cognitive performance at NorthShore (NS). We then used independent component analysis to identify PD cognition-related pattern (PDCP) and DMN topographies in resting-state fMRI (rs-fMRI) data from an independent population in Berlin (n=23). The spatial relationship of the two topographies was determined at the subnetwork level. The topographies were further compared to previously described PDCP networks from NS to evaluate their consistency across cohorts, imaging platforms, and medication state.

Results

Cognitive impairment in PD is associated with increases in metabolic PDCP expression and reflects partial loss of DMN activity. We identified a fPDCP topography in an independent cohort scanned with rs-fMRI in the on-medication state. fPDCP_BERLIN expression correlated with verbal memory performance and was elevated in PD patients with MCI compared to their counterparts without cognitive deficits. This topography resembled the previously described PDCP_NS patterns from FDG PET and rs-fMRI data scanned in the off-medication state. The rs-MRI analysis uncovered that PDCP selectively involves the ventral DMN subnetwork (precuneus and PCC), while the anterior and posterior subcircuits of the DMN are not affected. Importantly, the PDCP goes beyond the DMN topography with activity changes in dorsolateral prefrontal and medio-temporal areas that are unrelated to the DMN space.

Conclusions

The findings show that the PDCP is a reproducible cognition-related network that is topographically distinct from the DMN. The utility of the PDCP as a network biomarker of cognitive dysfunction in PD is further highlighted by its independence of imaging platform and treatment condition.

Thursday, September 23rd, 16:00 [Symposium: Metabolic Brain Imaging in Neurodegenerative Disorders]

Metabolic correlates in PSP clinical subtypes

Gloria Martí-Andrés(1), Liza Van Bommel(2), Elena Prieto(1), Rafael Valentí(1), Laura Armengou-García(1), Mario Riverol(1), Sanne Meles(2), Rosalie Kogan(2), Remco Renken(2), Vita Gurvits(2), Teus Van Laar(2), Marco Pagani(3), M Rosario Luquin(1), Klaus Leenders(2), Javier Arbizu(1)

1 Clínica Universidad de Navarra, Pamplona, Spain. 2 University Medical Center Groningen, Groningen, Netherlands. 3 Institute of Cognitive Sciences and Technologies, Rome, Italy.

Objective: To evaluate brain glucose metabolic abnormalities in patients with a clinical diagnosis of PSP variants.

Methodology: We performed a retrospective, multicenter cohort study on 73 PSP patients who were referred for a FDG-PET scan: PSP-RS n=46; PSP-P n=19; and PSP-PGF n=8. We included 55 HC and 58 PD patients as reference groups. We analyzed the regional differences in metabolism between the groups using two analytical approaches (SPM and SSM/PCA). Additionally, we obtained a PSP related pattern (PSPRP) and then cross-validated in independent populations at the individual level.

Results: Compared to HC, analyses showed relative hypometabolism in the midbrain, basal ganglia, thalamus and fronto-insular cortices, and relative hypermetabolism in the cerebellum, sensorimotor and posterior insula cortices associated with PSP. Compared to PD, the metabolic abnormalities in PSP were similar but involved more severe hypometabolism in the putamen and globus pallidus, and hypermetabolism in the occipital cortices. The PSPRP obtained showed optimal diagnostic accuracy to distinguish between PSP and HC and between PSP and PD. Moreover, PSP-RS and PSP-P patients showed significantly more PSPRPs expression than PD and HC.

Conclusions: The glucose metabolism assessed by FDG-PET is a useful and reproducible supportive diagnostic tool for PSP in different populations and PSP variants.

Thursday, September 23rd, 16:00 [Symposium: Metabolic Brain Imaging in Neurodegenerative Disorders]

Specific Metabolic Brain Patterns in Alzheimer's dementia and dementia with Lewy bodies

Matej Perovnik(1,2), Petra Tomše(3), Luka Ležaić(1,3), Maja Trošt(1,2,3)

1 Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

2 Department of Neurology, University Medical Center Ljubljana, Ljubljana, Slovenia

3 Department of Nuclear Medicine, University Medical Center Ljubljana, Ljubljana, Slovenia

Aims: To identify dementia with Lewy bodies related pattern (DLBRP) and to investigate its relationship with previously identified Alzheimer's dementia related pattern (ADRP).

Methodology: We applied a network analysis (scaled subprofile model/principal component analysis - SSM/PCA) on FDG PET scans from 20 DLB1 and 20 normal controls (NC1) for DLBRP identification. The procedure was first performed on the unmodified subjects' scans and then also on scans from which ADRP was removed by an orthogonalization. Furthermore, we removed DLBRP from ADRP. Expressions of newly identified DLBRP, DLBRP-orthoADRP, ADRP and ADRP-orthoDLBRP were calculated on a validation group of 60 DLB2, 21 NC2 and 63 biomarker-confirmed AD patients.

Results: Expression of ADRP, characterized by reduced metabolism in temporoparietal cortices, thalami and precuneus with relative increases in the cerebellum and pons, was elevated in AD and DLB patients. DLBRP expression, characterized by reduced metabolism in parietal and occipital cortices and precuneus with relative increases in the cerebellum and pons was significantly higher in DLB patients compared to NC and to AD patients. DLBRP could only modestly distinguish between the two dementias (AUC = 0.71). Based on the expression of DLBRP-orthoADRP, characterized by reduced metabolic activity in the occipital cortices and preserved metabolic activity in temporal cortices and posterior cingulum, we could accurately distinguish between the two groups (AUC = 0.89). Based on the expression of ADRP-orthoDLBRP, characterized by reduced metabolic activity in temporal, parietal and frontal cortices and preserved metabolism in occipital cortices and anterior cingulate cortex we could moderately distinguish the two groups (AUC = 0.77).

Conclusions: DLBRP-orthoADRP can best distinguish between AD and DLB among the studied metabolic patterns. It may reflect the metabolic pattern related to core DLB pathology, after AD related pattern was removed.

Thursday, September 23rd, 16:00 [Symposium: Metabolic Brain Imaging in Neurodegenerative Disorders]

Correlations between brain metabolism and neuropathology in sporadic Creutzfeldt-Jakob disease

Tomaž Rus (1,2), Jernej Mlakar (3), Mara Popović (3), Luka Ležaić (4), Milica Kramberger (1,2), Zvezdan Pirtošek (1,2), Maja Trošt (1,2,4)

1 Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

2 Department of Neurology, University Medical Center Ljubljana, Ljubljana, Slovenia

3 Institute of Pathology, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

4 Department of Nuclear Medicine, University Medical Center Ljubljana, Ljubljana, Slovenia

Backgrounds: Sporadic Creutzfeldt-Jakob's disease (CJD) is a progressive neurodegenerative disorder characterized by rapidly progressing dementia with additional neurological signs. Final diagnosis is possible only by pathohistological examination of brain tissue which is obligated by law in case of any clinical suspicion. Due to short disease duration and availability of final pathological diagnosis CJD may be considered an in vivo model of neurodegeneration. The aim of our study was to correlate brain metabolism measured by FDG-PET in a living CJD patient with histopathological changes post mortem. **Methods:** 16 CJD patients and 16 normal controls (NC) underwent brain FDG-PET imaging. Images were spatially normalized and smoothed in SPM5 software and region-of-interest analysis was performed using MarsBar toolbox for SPM. Twelve strategic regions (on the left side) were chosen based on previous research. Each region was independently standardized (z-scored) according to NC. In all 16 CJD patients final diagnosis was confirmed at pathohistological examination. At autopsy brain samples were obtained from the same twelve strategic regions, paraffin embedded and histologically (hematoxylin-eosin; HE) or immunohistochemically processed (IHC; using anti-PrP12F10 antibody against PrPsc protein and anti-HLA-DR antibody to detect activated microglia). All the HE samples (16 x 12) were examined for vacuolization and subjectively scored by three independent examiners according to the number of vacuoles (estimated 0-3). All the IHC samples (16 x 12 samples treated with anti-PrP12F10 antibody and 16 x 12 samples treated with anti-HLA-DR antibody) were assessed for PrPsc load and activated microglia by three independent examiners (estimated 0-3) and with automated machine-learning-based analysis of high-resolution scans of IHC samples using QuPath software (University of Edinburgh). Agreement among the three examiners was evaluated using single score intraclass correlation method using irr package run in R software. We investigated consistency of metabolic and pathologic changes in CJD patients (single score intraclass correlation analysis), correlated brain metabolism with pathohistological changes on group level and built multivariate mixed linear models to investigate relationship between brain metabolism and pathological changes on a single subject level. **Results:** Examiners achieved good agreement for HE, PrP12F10 and HLA-DR analysis. While there was a substantial consistence in brain metabolism in selected brain regions among CJD patients, vacuolization (HE changes) was more variable (fair consistency in vacuolization of regions) and there was even

more variability found in PrPsc load and activated microglia (slight consistency). Metabolic changes significantly correlated with vacuolization but not with PrPsc load and activated microglia on group level. However, multivariate mixed model analysis showed significant linear relationship between brain metabolism and vacuolization ($p < 0.0001$), activated microglia ($p = 0.004$) and nonsignificant relationship with PrPsc load ($p = 0.07$). **Conclusion:** Our study confirms robust changes in brain metabolism in CJD largely independent of special distribution of pathological changes. These findings indicate an existence of robust metabolic brain network specific for CJD despite pathological and clinical variability consistent with previous research.

Friday, September 24th, 13:00 [Symposium: Deep Brain Stimulation for movement disorders – A neuroimaging perspective]

Non-motor symptoms in Parkinson's disease and Dystonia: Neuroimaging perspective

Vladimira Vuletić

Clinical Department of Neurology, University Hospital Rijeka, Rijeka, Croatia

Our aim was to see the effect of Deep brain stimulation (DBS) on nonmotor symptoms in patients with dystonia and Parkinson's disease (PD).

We conducted investigation with anamnesis and treatments' data, Pittsburgh Sleep Quality Index (PSQI), PD Questionnaire-39, Parkinson's disease sleep scale (PDSS), Visual Analogue Scale, McGill questionnaire and Hospital Anxiety and Depression Scale (HADS), Montreal Cognitive Assessment (MoCA) and Mini Mental State Examination (MMSE), 36-Item Short Form Health Survey (SF-36), Functional Independence Measure (FIM) instrument, Unified Parkinson Disease Rating Scale (especially motor score and activities of daily living) (UPDRS), Burke-Marsden-Fahn Dystonia Scale (BMFDS). The study involved 30 patients with dystonia and 100 patients with PD treated by DBS. We did the basal testing before treatment and another investigation after 6 months.

After DBS in dystonia patients we observed significant decrease in frequency concerning sleep problems (from 80% to 10% of patients), anxiety (from 50% to 30%), depression (from 56% to 25%) and pain (from 90% to 25%) ($p < 0.05$). The cognition was without any change in all patients (16% vs 17%).

In PD patients we found a significant reduction in frequency concerning pain (from 70% to 45%, $p < 0.05$), sleep problems (from 60% to 35%, $p < 0.05$) and anxiety (from 75% to 45%, $p < 0.05$) but in cognition (from 30% to 27%) and depression (45% to 35%) was not significant after DBS.

DBS helps in relieving of the pain, sleep and mood problems in dystonia and PD patients what improved their quality of life. Further randomized studies are needed to confirm these findings.

Friday, September 24th, 13:00 [Symposium: Deep Brain Stimulation for movement disorders – A neuroimaging perspective]

The effect of Deep Brain Stimulation on Brain Metabolism in Movement Disorders

Maja Trošt

**Department for Neurology and Department for Nuclear Medicine UMC Ljubljana
Medical Faculty, University of Ljubljana**

Deep brain stimulation (DBS) is a neuromodulation therapy routinely used as a non-pharmacological treatment of patients with a variety of neurological and psychiatric disorders.

Brain glucose metabolism is a proxy of synaptic activity and can be evaluated with FDG PET, which enables clinicians to improve early differential diagnosis, monitor disease progression, assess treatment effects, and predict functional recovery of novel experimental therapies. FDG PET can also provide neuroimaging correlates of clinical response to DBS and offer an insight on mechanisms of action of DBS treatment.

Movement disorders represent a variety of neurodegenerative diseases with progressive motor and cognitive dysfunction involving cortico-striato-pallido-thalamocortical (CSPTC) circuits. A disease specific metabolic brain patterns have been identified by the network analysis of FDG PET images. For example, Parkinson's Disease Related Pattern (PDRP), which was associated with motor features and Parkinson's Disease Tremor Pattern (PDTP) associated with tremor in PD. Both patterns reflect widely distributed network abnormality in the CSPTC and cerebello-thalamo-cortical pathways respectively. Studies have shown that DBS of STN and GPi suppresses the expression of PDRP. Further, PDRP expression was reduced with STN DBS but not with Vim DBS. On the other hand, PDTP network activity declined in both Vim and STN DBS groups, however greater PDTP modulation was achieved with Vim DBS.

These are only few examples of how FDG PET and the applied network analytical approaches evaluate DBS related changes in brain metabolism.

Friday, September 24th, 13:00 [Symposium: Deep Brain Stimulation for movement disorders – A neuroimaging perspective]

Parkinson's disease as a network disorder: Lessons from connectivity studies

Rok Berlot

Department of Neurology, University Medical Centre Ljubljana

The link between the cardinal motor symptoms of Parkinson's disease (PD) and progressive degeneration of dopaminergic neurons in the nigrostriatal pathway has been firmly established. However, neuroimaging studies suggest that activity in multiple brain regions correlates

with motor symptoms of PD. Less is known about the mechanisms underlying non-motor and cognitive manifestations of the disease, which might depend on structural decline of distinct grey matter areas as well as functional alterations of distributed brain networks. In this presentation, we will discuss some neuroimaging correlates and predictors of PD symptoms with an emphasis on brain network measures. Further, we will examine cases where focal lesions in various brain locations lead to parkinsonism to establish a role of a distributed brain network in parkinsonism. Next, we will turn to treatment with deep-brain stimulation which - through affecting a single network node – impacts the whole-brain network. Finally, we will discuss how network imaging approaches can be utilised to guide treatment with deep-brain stimulation.

Friday, September 24th, 13:00 [Symposium: Deep Brain Stimulation for movement disorders – A neuroimaging perspective]

Frequency modulation in deep brain stimulation: Does it work and is there neuroimaging proof of its action?

Dejan Georgiev

Department of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia

Deep brain stimulation (DBS) of the subthalamic nucleus (STN-DBS) and globus pallidus pars interna (GPi-DBS) are now well-established treatment options for movement disorders, including Parkinson's disease (PD) and dystonia. Even though there is no doubt in the long-term clinical benefits of the STN-DBS in PD patients and GPi-DBS in dystonia there are certain side effects of DBS, such as gait abnormalities, postural instability, falls, dysarthria in PD and parkinsonian symptoms in dystonia.

Frequency of stimulation (FS), in addition to other parameters (amplitude, pulse width, contact configuration), has been shown to have an important impact on certain clinical aspects of PD and dystonia. FS, unlike the other parameters, has a more specific mechanism of action. Namely, while high frequency stimulation (HFS, > 100 Hz) is usually effective in controlling the appendicular symptoms of the disease (bradykinesia, tremor, rigidity), it can often worsen axial symptoms (gait, postural instability, dysarthria). Low frequency stimulation (LFS, < 100 Hz) might be beneficial for the treatment of these symptoms. Only few studies have explored the effect of LFS in dystonia patients, which suggest that LFS might be beneficial in the treatment of the main symptoms in dystonia. However, the results of the studies in both, PD and dystonia are inconsistent, the methodologies used differ, and the mechanisms of LFS action are not clear. In addition to making an overview of the clinical aspects of the use of LFS in DBS for movement disorders, in this presentation we will also focus on the possible mechanisms of of LFS with an emphasis of the use of imaging in the study of LFS mode of action.

Friday, September 24th, 13:00 [Symposium: Deep Brain Stimulation for movement disorders – A neuroimaging perspective]

Impulsivity in STN-DBS PD: More than a unitary phenomenon

Tjaša Mlinarič, Dejan Georgiev

Department of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia

Along with the obvious motor problems, patients with Parkinson's disease (PD) develop a number of non-motor deficits, which challenge their daily activities. Impulsive behaviors are common non-motor complications in PD patients, and they are usually attributed to the treatment of PD. Both dopaminergic medication and deep brain stimulation of the subthalamic nucleus (STN-DBS) have been previously shown to affect impulsivity in several domains.

The aim of our study was to establish how three impulsivity domains are affected in patients with PD relative to dopaminergic medication and STN-DBS treatments. To answer this question, we assessed patients with PD and healthy controls on different impulsivity measures in several conditions. With our research, we hoped to disentangle between different effects of medication and STN-DBS treatment on impulsivity and to contribute to the understanding of the post-treatment functioning of PD patients in their daily living.

Friday, September 24th, 13:00 [Symposium: Deep Brain Stimulation for movement disorders – A neuroimaging perspective]

Effects of subthalamic nucleus deep brain stimulation on language in advanced Parkinson's disease

Živa Drakulić¹, Christina Manouilidou², Maja Trošt¹

**1 Department for Neurology, UMC Ljubljana, Slovenia
2 Department of Comparative and General Linguistics, Faculty of Arts, University of Ljubljana, Slovenia**

Deep brain stimulation of subthalamic nuclei (STN DBS) is an established surgical treatment for motor symptoms in advanced Parkinson's disease (PD). The improvement of motor function as measured by Unified Parkinson's disease rating scale (UPDRS) has been consistently determined after STN DBS (1). However, the effects of STN DBS on cognitive and other non-motor functions are less studied and its mechanisms of action are still poorly understood (2). PD and STN DBS treatment can both impair language (3, 4). Various language domains seem to be altered in PD: speech, processing of syntax and grammar, production, fluency, action words, pausing and non-verbal communication (4). On the other hand, STN DBS might cause cognitive adverse events such as worsened verbal fluency, executive dysfunction and decreased attention. These may all impair language processing and production in PD patients (3). Other studies have shown that STN DBS improves language processing, such as performance in lexical decision and naming tasks for action related words (5–7). We plan to determine specific domains of language dysfunction in PD patients, its mechanism, and the effect of STN DBS

treatment on language skills. To reach this goal, various language tasks in Slovenian language as well as structural and functional brain imaging will be applied to PD patients treated with standard treatment and STN DBS.

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Saturday, September 25th, 13:00 [Symposium: Music and Brain: Evidence-based music interventions in medicine]

Neurology of Music and Brain

Daniele Schoen, PhD

Aix-Marseille University, France

How does the brain work? No one knows. What is certain is that it allows us to interact with the world. A dynamical system perspective, with complex oscillatory dynamics visible in the cerebral rhythms, may allow to explain how the brain quickly adapts to the external ever-changing context. Nevertheless, the brain does not process the entire sensory experience, but rather the difference between the input and an internal model of the world. Our priors about the world become very important. Changing priors will change our perception of the world. Music is a good model to address the coupling between brain activity and the surrounding world. It is temporally and spectrally structured and it requires to anticipate with precision in time (rhythm) and in content (harmony) as well as to flexibility and quickly adapt to changes. In this perspective, music making, by modifying the oscillatory properties of complex neural networks, may improve the ability to anticipate, which in turn will affect other cognitive nonmusical skills.

Saturday, September 25th, 13:00 [Symposium: Music and Brain: Evidence-based music interventions in medicine]

The mother's voice, singing and speaking, as a special tool for early interventions in the NICU

Manuela Filippa, PhD

University of Geneva, Switzerland

It is now clearly established that the environment and the sensory stimuli, particularly during the perinatal period, have an impact on infant's development. During the last trimester of gestation, activity-dependent plasticity shapes the fetal brain, and prematurity has been shown to alter the typical developmental trajectories. In this delicate period, preventive actions aiming at modulating these developmental trajectories through activity-inducing interventions are currently underway to be tested. Our purpose is to describe the potentialities of early vocal contact and music for supporting the preterm infant's development, and their potential beneficial effect for example on pain protection.

Scientific evidence supports a behavioral orientation of the newborn to organized sounds, such as those of voice and music, and recent neuroimaging studies further confirm full cerebral processing of music as multisensory stimuli. However, the impact of long-term effects of music exposure and early vocal contact on preterm infants' long-term neurodevelopment needs be further investigated. Research projects are currently on the way to fill this gap in knowledge.

Saturday, September 25th, 13:00 [Symposium: Music and Brain: Evidence-based music interventions in medicine]

Heart rate variability in relation to self-selected music or music genres pre-selected by the researchers

Uroš Kovačič, MD, PhD, and Maja Derlink, PhD

Institute of Pathophysiology, University of Ljubljana, Faculty of Medicine, Zaloška 4, Ljubljana, Slovenia

Listening to music is a complex phenomenon, involving psychological, emotional and physiological responses, such as heart contractility, heart rate, heart rate variability (HRV), blood pressure and respiratory rate. HRV, variation in interbeat intervals, is a measure of autonomic nervous system (ANS) activity. Some HRV parameters can be used as an index of cardiac vagal tone. Previous studies of physiological effects elicited by different music genres show that tempo affects the arousal, whereas major/minor mode affects mood. Nevertheless, due to application of very heterogeneous musical stimuli in different studies, there is inconsistency when the effects of specific musical stimuli on ANS are being determined along with corresponding cardiovascular changes. Our aim was to measure the effects of music listening on the modulation of ANS via measurement of HRV. Healthy adult volunteers were exposed to music listening via headphones in a supine position. Each person participated in three recording sessions, with distinct protocols: 1) preselected music comprised of four

different genres (classical music, baroque music, Gregorian chants and ambient music), 2) participant self-selected music and 3) silent control. Music chosen by the participants varied greatly compared to preselected music chosen by the researchers in terms of tempo, genre and elicited arousal. Participants reported self-selected music to be more pleasant than music chosen by the researchers. Listening to music (reactivity phase) showed a trend in decreasing activity of the parasympathetic (vagal) ANS function when compared to baseline conditions (resting HRV) or when compared to control protocol (silence). Notably, HRV parameters, indicating higher parasympathetic (vagal) tonus in the recovery phase after music listening, increased significantly when compared to the reactivity phase during music listening. Music listening has future perspectives as a simple non-pharmacological method to modulate the listener's ANS function in a clinical setting.

Saturday, September 25th, 15:00 [Symposium: Brain health across the lifespan – Findings from the Lifebrain project]

Ageing and brain imaging in Lifebrain

Klaus P. Ebmeier for Lifebrain Consortium

Department of Psychiatry, University of Oxford, UK

While classical mechanisms underlying Alzheimer pathology have not been generating effective interventions, a more broad-based approach to biological markers of cognitive deterioration is of interest. Similarly, relatively non-specific exposures, such as to risk factors for vascular disease and metabolic syndrome or diabetes appear to predict development of degenerative dementia. The Lifebrain Consortium consists of European Cohort Studies, including approximately 8000 MRI scans in 5000 participants [1]. Brain measurements have been used to predict chronological age, using the residual of the regression to define a "brain age gap", defining the individual brain as either biologically older or younger than its chronological age. "Brain age" suggests a dynamic process, capturing the speed of aging. However, Lifebrain data have shown that brain age relates to early life factors, such, as birth weight and polygenic scores, but not to accelerated brain aging [2]. Similarly, educational attainment which is often related to cognitive or "brain reserve", appears not to influence brain ageing [3]. In contrast, education was positively related to intracranial (ICV) and total brain grey matter (GM) volume in US and European cohorts, while socioeconomic stratum or income was more strongly related to brain and cognition in US than European cohorts [4].

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Saturday, September 25th, 15:00 [Symposium: Brain health across the lifespan – Findings from the Lifebrain project]

What can blood biomarkers tell us about the brain?

Christian A. Drevon & Thomas E. Gundersen

Vitas Ltd. Oslo Science Park, Gaustadalléen 21, 0349 Oslo, Norway

Several hundred markers of diet, inflammation, and some risk factors of disease are analyzed by Vitas Ltd – a Norwegian contract laboratory, which is member of the Lifebrain consortium. Vitas has extensive experience with most types of biological material also collected on dried blood spots (DBS) making sampling much cheaper, more convenient and applicable in the field. Combining biomarkers from blood, brain imaging and cognitive tests may provide new approaches to brain biology.

It is not surprising that several well-known markers of cardiac health also seem to be relevant for brain health. Thus, blood lipids like essential fatty acids, cholesterol and triacylglycerols, and glucose and vitamin D3, are associated with anatomical as well as functional aspects of the brain. From some preliminary data it seems to be a link between a certain class of lipids named diacylglycerols and sleep, although it turns out to be much more complicated than expected from a few previously published studies.

Saturday, September 25th, 15:00 [Symposium: Brain health across the lifespan – Findings from the Lifebrain project]

What is brain health? Perceptions of respondents to the Global Brain Health Survey

Isabelle Budin-Ljøsne for Lifebrain Consortium

Department of Genetics and Bioinformatics, Norwegian Institute of Public Health, Oslo, Norway

Brain health has recently been launched as a concept encompassing brain integrity, mental health and cognitive health. Maintaining a healthy brain is essential for individual well-being and functioning. The Global Brain Health Survey collected data about people's perceptions of brain health, and willingness to take care of their brain by adopting new lifestyles [1]. The survey was conducted online and translated into 14 languages and collected 27,590 responses from 81 countries. In this talk, survey results on how respondents perceived the concept of brain health will be presented, with particular focus on results relating to: (1) factors respondents believed to influence brain health, (2) life periods considered important to look after one's brain, and (3) diseases and disorders associated with the brain. Differences between demographic groups will be investigated and implications for health policy raised. Preliminary insights into which actions respondents are willing to undertake to maintain a healthy brain will also be presented.

[1] Budin-Ljøsne I, Friedman BB, Suri S, et al. The Global Brain Health Survey: Development of a Multi-Language Survey of Public Views on Brain Health. *Front Public Health*. 2020 Aug 14;8:387. doi: 10.3389/fpubh.2020.00387.

Saturday, September 25th, 15:00 [Symposium: Brain health across the lifespan – Findings from the Lifebrain project]

Brain asymmetry in aging and Alzheimer's disease

James M. Roe

Department of Psychology, University of Oslo, Norway

Aging and Alzheimer's Disease (AD) are accompanied by large-scale alterations in brain organization, and brain changes accelerated in AD may occur gradually over the lifespan – suggesting dimensionality between aging and AD. Although structural asymmetry is an organizing feature of the cerebral cortex, it is not known whether or how continuous age- and AD-related cortical degradation alters cortical asymmetry. Thus, the foundational question of whether and where the cerebral hemispheres atrophy at different rates in aging and AD remains open.

Applying novel analyses in Lifebrain's longitudinal adult lifespan cohorts, we uncover a new principle of brain aging, and find evidence to suggest that brain changes in normal aging and AD may at least partly exist on a continuum – highlighting the importance of lifespan perspectives for understanding the pathophysiology of AD.

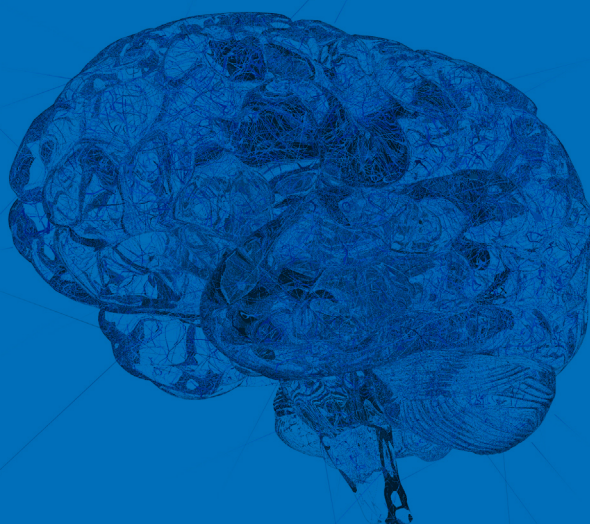


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Effect of repetitive transcranial magnetic stimulation on language performance in Alzheimer's Disease: a Slovene-speaker case study

Georgia Roumpea (a), Katarina Marjanovič (a), Tjaša Mlinarič (b), Zvezdan Pirtošek (b), Jure Bon (c), Christina Manouilidou (a)

(a) Department of Comparative and General Linguistics, University of Ljubljana, Ljubljana, Slovenia. (b) Department of Neurology, University Medical Centre, Ljubljana, Slovenia. (c) Psychiatric Clinic, Ljubljana, Slovenia.

We investigated the effect of repetitive transcranial magnetic stimulation (rTMS) on production of simple and derived words, and lexical decision in a Slovene-speaker with AD. rTMS has been found to have positive effects on naming in AD, but while previous studies have focused on the dissociation between objects and verbs, deverbal forms (agent bralec 'reader' and process branje 'reading' nominalizations) have not been examined. Moreover, to our knowledge, the effect of rTMS on accuracy and reaction time (RT) on lexical decision task, as well as accuracy in derivation task, is addressed for the first time in the rTMS in AD literature. Intervention: high-frequency rTMS over the DLPFC bilaterally for 3 weeks (5/week). Method: naming, derivation by definition, online and offline lexical decision tasks. Participant: one female diagnosed with mild AD. Results: Participant's average accuracy was slightly increased at the post-treatment evaluation on both naming (80% vs. 90%) and offline LDT (93% vs. 96%) tasks. Regarding the naming conditions, a high increase in the accuracy was mainly observed in the categories of agent and process nominalizations (75% vs. 95%; 60% vs. 90%, respectively). On the derivation task, a slight decrease was observed in participant's performance post-treatment (97 % vs. 91%). Participant's accuracy in the online LDT was highly increased post-treatment (73% vs. 95%) and her average RT was improved (2281ms vs. 1445ms). Discussion: rTMS appears to improve accuracy in naming and LDT tasks. It also positively influenced LDT latency by speeding RT. Further research is needed for more accurate results.

Keywords: rTMS, Alzheimer's disease, naming, derivation, lexical decision

The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog): standardisation of Slovenian version

Janina Ulbl, Martin Rakusa

Department of Neurology, University Medical Centre Maribor, Slovenia

Introduction: number of patients with Alzheimer's disease rapidly increases worldwide. ADAS-Cog is an eleven-task screening tool developed for detecting early cognitive changes due to Alzheimer's disease. A higher total score correlates with more significant cognitive impairment. Our study aim was to standardise ADAS-Cog for the Slovenian population.

Methods: we included 84 cognitively unimpaired people who were tested with the Slovenian version of ADAS-Cog. Descriptive statistics for demographic data, score on each ADAS-Cog task, and total score were calculated. Mean values for each task and total score were compared between sexes and people younger or older than 65 years. In the end, we create a linear model between the ADAS-Cog total score and sex, age, and years of education.

Results: mean age was 67.3 (SD 11.1) years, mean years of education 12.5 (SD 2.8) years, and mean total score 7.4 (SD 2.3) points. There were no differences between sexes in demographic data or ADAS-Cog score at a single task or in total. A significant difference was found in the total score between younger and older participants (5.9; SD 1.6 vs 8.2 SD 2.3). With linear regression, we found that the total score was significantly influenced by age ($B=0.138$, $p<0.001$) and years of education ($B=-0.236$, $p=0.018$).

Conclusion: we standardised ADAS-Cog for the Slovenian population. The total score for cognitively unimpaired people is relatively low and is following similar studies. However, older people with lower education may achieve lower scores than the rest of the population.

Keywords: Alzheimer's disease, cognitive impairment, cognitive tests

DNA methylation of candidate genes BDNF and COMT in Alzheimer's disease

Matea Nikolac Perković¹, Katarina Kouter², Dubravka Švob Štrac¹, Mojca Katrašnik², Suzana Uzun^{3,4}, Oliver Kozumplik^{3,4}, Ninoslav Mimica^{3,5}, Nela Pivac¹, Alja Videtič Paska²

¹ Laboratory for Molecular Neuropsychiatry, Division of Molecular Medicine, Ruder Boskovic Institute, HR-10000 Zagreb, Croatia.

² Medical Center for Molecular Biology, Institute of Biochemistry and Molecular Genetics, Faculty of Medicine, University of Ljubljana, SI-1000 Ljubljana, Slovenia.

³ University Psychiatric Hospital Vrapce, HR-10090 Zagreb, Croatia

⁴ School of Medicine, Josip Juraj Strossmayer University of Osijek, HR-31000 Osijek, Croatia

⁵ University of Zagreb Medical School, HR-10000 Zagreb, Croatia

For diagnosis of Alzheimer's disease (AD) there are currently no validated biomarkers which can be used to accurately diagnose or to distinguish it from other dementia-causing neuropathologies. Tests based on molecular-genetic biology analysis are only entering the routine clinical practice, but are as are other clinical tests, relevant only after the disease has already made considerable progress. Epigenetic alterations, like DNA methylation, have been implicated in the pathogenesis of different human diseases, including AD.

In our study we applied contemporary methods (next generation sequencing, droplet digital PCR) and determined methylation status of AD candidate genes, COMT and BDNF, in white blood cells and circulating cell-free DNA (cfDNA) from plasma in clinically well-defined AD patients and subjects with mild cognitive impairment (MCI).

Using PCR-amplicon library preparation approach, we sequenced 9 amplicons residing in BDNF gene and 3 amplicons residing in COMT gene, covering 169 and 62 CpG sites, respectively. Changes were observed for both genes. Biggest change was observed in two BDNF amplicons (BDNF_3 and BDNF_9), located at the CpG islands in the promoter region and in the first intron of the BDNF gene. On average, we observed lower levels of methylation in both BDNF amplicons in patients with AD compared to subjects with MCI.

Our results suggest that further search for epigenetic marks of AD not only in the central nervous system, but also on the periphery, could provide some more information on molecular-genetic background of this complex disorder.

Keywords: Alzheimer's disease, epigenetics, DNA methylation, BDNF, COMT

Expression of Na⁺,K⁺-ATPase isoenzymes and myokines in cultured human myotubes innervated by rat spinal cord explants

Vid Jan¹, Katarina Miš¹, Natasa Nikolic², Klemen Dolinar¹, Metka Petrič¹, Andraž Bone¹, G. Hege Thoresen^{2,3}, Arild C. Rustan², Tomaž Marš¹, Alexander V. Chibalin^{4,5}, Sergej Pirkmajer^{1,*}

¹: Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia ²: Section for Pharmacology and Pharmaceutical Biosciences, Department of Pharmacy, University of Oslo, Oslo, Norway ³: Department of Pharmacology, Institute of Clinical Medicine, University of Oslo, Oslo, Norway ⁴: National Research Tomsk State University, Tomsk, Russia ⁵: Department of Molecular Medicine and Surgery, Integrative Physiology, Karolinska Institutet, Stockholm, Sweden *Presenting/corresponding author

Na⁺,K⁺-ATPase (NKA), a heterodimeric (α/β) ion pump and P-type ATPase, maintains transmembrane ion gradients and is essential for skeletal muscle excitability and contractility. Denervation reduces the NKA content in skeletal muscle, while reinnervation increases it. Primary human myotubes, a widely used model to study human skeletal muscle in vitro, are most commonly cultured without the presence of neurons and typically do not contract spontaneously. We have recently examined¹ whether the myotubes innervated by motor neurons from the embryonic rat spinal cord explants expressed higher levels and/or a different pattern of NKA subunits (α and β) compared with the aneurally cultured myotubes. The auxiliary (regulatory) subunits of NKA (FXYP1 and FXYP5) as well as myokines, which are regulated by contractions, were also assessed. Myotubes innervated by rat spinal cords started to contract within 7-10 days, and had higher mRNA levels of myokines, such as IL-6, IL-7, IL-8, and IL-15, after 10-11 days of co-culture. The mRNA expression of NKA, FXYPs, and myokines, such as myostatin, cathepsin B, meteorin-like protein, or SPARC, remained similar between the innervated and aneural cultures. In 21-day-old co-cultures the protein abundance of NKAα1, NKAα2, FXYP1, and phospho-FXYP1(Ser68) was increased, while the mRNA levels of NKA subunits and myokines were similar to those in the aneural cultures. Suppression of the neuromuscular transmission with α-bungarotoxin or tubocurarine did not alter the NKA or FXYP mRNA expression. Collectively, our results show that gene expression of NKA isoenzymes in cultured human myotubes does not depend on innervation.

¹: Jan et al. PLoS One. 2021;16(2):e0247377.

Keywords: Na⁺,K⁺-ATPase, FXYP, cultured human myotubes, in vitro innervation, myokines

Saturday, September 25th, 11:00 [Poster section: Short Oral Presentations Session II]

Role of PDGFR α - Integrin interactions in Anoikis resistance mediated glioblastoma progression

Pampa Pain, Dr Prakash P. Pillai

Division of Neurobiology
Department of Zoology
Faculty of Science
The Maharaja Sayajirao University of Baroda
Vadodra, Gujarat - 390002 India

Glioblastoma Multiforme (GBM) is a highly aggressive and invasive solid tumor which occurs in the cerebral hemispheres of the Human brain. GBM tumor has a unique property of metastasizing to distant regions in the brain itself through anchorage independent growth, which induces anoikis resistance phenomena. Anchorage in cells is facilitated by many cell-cell and cell-ECM interacting proteins and one such family of proteins are Integrins, which are upregulated in many solid tumors. Interestingly, Integrins are found to be upregulated in GBM cells as well, and specifically involved in maintaining cell-cell interaction even in anchorage independent condition leading to cell survival and proliferation. Moreover, Integrins also interact with Growth Factor receptors, majorly receptors which belong to Tyrosine kinase family in regulating cell survival and proliferative pathways in solid tumors including GBM. RTK proteins such as PDGFR- α , a type of PDGFR (Platelet Derived Growth Factor Receptor), is overexpressed in most aggressive and invasive subtypes of GBM i.e., Proneural and Mesenchymal and leads to upregulation of the cell survival and proliferative pathways. In GBM, there is an upregulation of cholesterol synthesis, which leads to the increase in formation of transient membrane rafts known as lipid rafts. These rafts structures, sequesters Integrins and RTKs and elevate the expression of proteins involved in downstream signaling of cell survival and proliferative pathways. However, it is not quite well understood how these lipid rafts are playing an important role in Anchorage independent induced Anoikis resistance regulated by PDGFR- α -Integrin interaction in inducing cell survival mechanism.

Keywords: Anoikis resistance, PDGFR-AA, Integrins and Glioblastoma Multiforme

Saturday, September 25th, 11:00 [Poster section: Short Oral Presentations Session II]

HMGB1 inhibition attenuates lipopolysaccharide (LPS)-induced neuroinflammation, cognitive dysfunction and sickness behavior

Devlina Ghosh¹, Aditi Singh¹, Alok Kumar³, Neeraj Sinha²

1Amity Institute of Biotechnology, Amity University
Uttar Pradesh, Lucknow Campus, Gomti Nagar Extension, Lucknow 226028, India
2 Centre of Biomedical Research, SGPGIMS-Campus,
Raibareli Road, Lucknow 226014, India.
3 Department of Molecular Medicine and Biotechnology, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, India.

Glycyrrhizin (GL), a natural component extracted from licorice (*Glycyrrhiza glabra*) root/rhizomes, is an antagonist of HMGB1. Chemically a triterpene glycol, GL has been administered in traditional clinical practices as an anti-inflammatory/antiviral since ages to treat chronic hepatitis cases. Recent studies have shown that GL binds directly to box A and box B of HMGB1 while inhibiting its chemotactic and mitogenic activity. It has been found that GL reduces the level of oxidative stress by increasing the level of antioxidants and reducing the oxidation in case of focal cerebral ischemia. However that partly answers the anti-inflammatory property associated with GL, in our study we found that that GL attenuates the adverse effects of neuroinflammation/sickness behavior and improves the functional outcome. We demonstrate that in vitro and in vivo LPS stimulated subjects show extensive release of nitrite, an inflammatory signal, while the same subjects when treated with GL, show significant reduction in nitrite release indicating neuroinflammatory regulation. In accordance, the secretion of reactive oxygen species is also dropped when LPS induced cells are exposed to GL. Furthermore, the release of proinflammatory cytokines in LPS induced BV2 cells as well as mice model, takes a plunge in presence GL thus regulating the microglia proinflammatory response. Our behavioral study support the fact that GL treatment improves the cognitive function while reducing anxiety/ depressive symptoms in LPS induced neuroinflammatory mouse model. Thus targeting HMGB1 using GL, presents a promising therapeutic possibility for regulating neuroinflammatory response and improving the outcome in neurobehavioral dysfunction.

Keywords: Glycyrrhizin, neuroinflammatory response, proinflammatory cytokines

Saturday, September 25th, 11:00 [Poster section: Short Oral Presentations Session II]

Educated vs. lay public view of neuroscience and science based brain health recommendations in Slovenia

Matej Perovnik (1,2,3), Nastja Tomat (1, 4), Gaj Vidmar (3, 5, 6), Vesna Van Midden (1, 2), Sara Fabjan (1, 7), Hana Hawlina (1), Dolores Trol (1), Alina Holnthaner (1), Sebastijan Krjnc (1), Maruša Grešak (1), Liza Žerdin (1), Judita Vidmar (8) and Mara Bresjanac (1, 3)

1 SiNAPSA, Slovenian Neuroscience Association, Slovenia

2 Department of Neurology, University Medical Centre, Ljubljana, Slovenia

3 Faculty of Medicine, University of Ljubljana, Slovenia

4 Institute for the Deaf and Hard of Hearing (Ljubljana), Slovenia

5 University Rehabilitation Institute (Slovenia), Slovenia

6 Department of Psychology, Faculty of Mathematics, Natural Sciences and Information Technologies, University of Primorska, Slovenia

7 Faculty of Health Sciences, University of Primorska, Slovenia 8 UMNI Institute, Ljubljana, Slovenia

The aim of our study was to gain insight into Slovenian public view on science based recommendations for brain health and neuroscience. Within the project “Z možgani za možgane” (Aim for the brain) we have conducted a survey that was filled out in part or completely by 2568 participants. The responders were divided into two separate subgroups based on their brain-related education (current or former). Responders, $n = 1012$, that were not nor had they ever been engaged in formal education about the brain nor they professionally relied on knowledge about the brain were considered to represent the lay public and key findings were recently reported (1). The remaining responders, $n = 1438$, were considered to represent a specifically educated group. Here we will present the views of neuroscience and science based brain health recommendations of this, specifically educated, subgroup and draw comparisons with lay public view. We will analyse similarities and differences between self-declared lay and educated responders to test the hypothesis that knowledge gap underlies possible differences in behaviour aimed at maintaining brain health.

Keywords: Health Literacy, Public Engagement, Brain Disorders, Brain health

Saturday, September 25th, 11:00 [Poster section: Short Oral Presentations Session II]

Physicians' standpoints for the use of music-based interventions in Slovenian health care system

Ana Kuder, Manca Kok, Saška Rakef, Igor Mihael Ravnik

B-AIR (all authors)

University of Primorska (Ana Kuder)

Leiden University (Manca Kok)

As a part of the interdisciplinary project B-AIR (Creative Europe, intended to create sound, voice and music programmes for babies and vulnerable groups of any age), a plan was developed to sensitize the medical community and general public to consider music as a relevant agent in health care. A study was designed with the main goal of finding out the interest and motivation to introduce the use of music in the health care system among Slovenian physicians. The pilot version of the questionnaire has already been administered to a smaller group of Slovenian physicians, known for their active interest in music. The preliminary results show a moderate interest and knowledge about the benefits of using music in Slovenian health care and limited current use of music by the respondents. Many respondents expressed the beneficial use of music in neurorehabilitation and chronic pain syndromes. Some of the respondents expressed willingness to work in a task force expected to be created as one of the results of the study and help with further development of the domain. A modified questionnaire will survey a larger medical population sample, and other professions allied to medicine, focusing specifically on the use of music in clinical practice and in research in neurology and psychiatry, in order to further explore the preliminary findings. The aim of the study is to get a more realistic picture of the knowledge and potential implementation of music in diverse settings. The results may be used for devising the most feasible future implementations.

Keywords: music-based interventions, Slovenian health care, interdisciplinary project

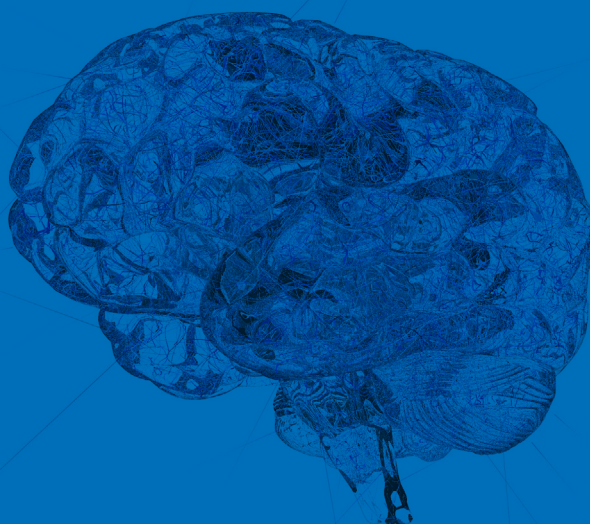


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Friday, September 24th, 15:00

Proteostasis Collapse: A Basis for Aging and Neurodegenerative Diseases

Richard I. Morimoto, PhD

Bill and Gayle Cook Professor of Biology Rice Institute of Biomedical Research Northwestern University Evanston, IL 60201 www.morimotolab.org

Aging is associated with the programmed decline of cell protective stress responses and the loss of cellular proteostasis essential to prevent the accumulation of misfolded and aggregated proteins common to all neurodegenerative diseases. We have employed multiple biological systems and approaches to identify the composition of the proteostasis network (PN) that regulates protein synthesis, folding, translocation and degradation, to demonstrate how the PN determines the stability and function of the proteome in health and fails in aging and diseases, and genetic and small molecule approaches to reset the PN and suppress aggregation and amyloid formation.

Our current efforts are to identify the earliest events that predict proteostasis failure in neurons and other tissues.

Friday, September 24th, 15:45

An update on Tau-related diseases

Gabor G. Kovacs, MD, PhD, FRCPC

University of Toronto, Department of Laboratory Medicine and Pathobiology and Tanz Centre for Research in Neurodegenerative Disease (CRND) Consultant Neuropathologist/Neurologist, University Health Network (UHN) <https://neuropath-ggkovacs.com> <https://www.tanz.med.utoronto.ca>

Filamentous deposits of known composition in brain cells define most human neurodegenerative conditions. Assemblies of the microtubule-associated protein Tau comprise the most frequent neurodegenerative proteinopathies. Diseases with filamentous Tau pathology can be divided into three groups, based on the isoforms in the filaments. In these diseases, be they sporadic or inherited, Tau is extensively modified post-translationally. The purpose of this presentation is to present a neuropathology-based approach to tau-related conditions and to highlight current hot topics of the field.

Friday, September 24th, 16:15

TDP-43 proteinopathies

Boris Rogelj

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are two ends of a phenotypic spectrum of disabling, relentlessly progressive and ultimately fatal neurodegenerative diseases. There is no cure for either of the diseases. Pathological hallmarks of the

overwhelming majority (95%) of ALS and over 60% of FTD cases, are cytoplasmic aggregation and nuclear clearance of otherwise nuclear TDP-43 protein defining them as TDP-43 proteinopathies. TDP-43 positive cytoplasmic inclusions have also been described in 57% of Alzheimer disease cases, 20% of Dementia with Lewy bodies and in a variety of other neurodegenerative conditions. Conversely, the TDP-43-negative pathology is defined mainly by aggregations of proteins FUS (ALS and FTD) or SOD1 (ALS) or tau (FTD). However, mutations in TDP-43 and FUS are uncommon in ALS and account for only up to 5% of familial and 1-5% of sporadic ALS cases and are very rare in FTD. In light of this, one of the most important questions in this field is what makes wildtype TDP-43 (or FUS) mislocalize and aggregate. The answer lies in the age and disease related changes of their de novo expression, modification, localization and/or degradation. These changes may also arise from disease-causing mutations in other genes, principal among which is the TDP-43 proteinopathy associated GGGGCC ((G4C2)_n) hexanucleotide repeat expansion (HRE) mutation in C9ORF72.

Friday, September 24th, 16:45

Now it is time for research to crack Parkinson's disease

Patrik Brundin, M.D. Ph.D.

Deputy Chief Scientific Officer, Van Andel Institute Director, Parkinson's Disease Center, Department of Neurodegenerative Science, Van Andel Institute, Grand Rapids, MI, USA <https://patrikbrundinlab.vai.org/overview/>

Parkinson's disease research has reached a very exciting time where we know more about the molecular underpinnings of the disease than ever before. The accumulation of aggregated proteins, the loss of mitochondrial function and the development of neuroinflammation all seem to play a role. By targeting these processes we hope that novel therapies can slow the rate of disease progression.

Friday, September 24th, 17:15

Huntington's disease

Roger A. Barker, BA, MBBS, MRCP, PhD

Wellcome - MRC Cambridge Stem Cell Institute and Department of Neurology, University of Cambridge, UK <http://www.thebarkerwilliamsgraylab.co.uk>

History, diagnosis, clinical features, pathogenesis and current and future treatment of Huntington's disease will be presented.

Work funded by the HDA; NIHR; ABN; EU; CHDI; Rosetrees trust and Evelyn Trust

Friday, September 24th, 17:45

Transmissible Spongiform Encephalopathies

Adriano Aguzzi, MD, PhD, DVM, hc FRCPATH

MD, PhD, DVM, hc FRCPATH, Institute of Neuropathology, University Hospital of Zürich Schmelzbergstrasse 12, CH-8091 Zürich, Switzerland <https://new.usz.ch/fachbereich/neuropathologie/>

Transmissible spongiform encephalopathies (TSEs) are neurodegenerative diseases of humans and many animal species caused by prions. The main constituent of prions is PrP^{Sc}, an aggregated moiety of the host-derived membrane glycolipoprotein PrP^C. Prions were found to encipher many phenotypic, genetically stable TSE variants. The latter is very surprising, since PrP^C is encoded by the host genome and all prion strains share the same amino acid sequence. Here I will review what is known about the infectivity, the neurotoxicity, and the neuroinvasiveness of prions. Also, I will explain why I regard the prion strain question as a fascinating challenge – with implications that go well beyond prion science. Finally, I will report some recent results obtained in my laboratory, which is attempting to address the strain question and some other basic issues of prion biology with a “systems” approach that utilizes organic chemistry, photophysics, proteomics, and mouse transgenesis.

Friday, September 24th, 18:15

A structural biologist's view of neuroscience

Holger Wille, PhD

Associate Professor, University of Alberta, Department of Biochemistry & Centre for Prions and Protein Folding Diseases & Neuroscience and Mental Health Institute

Alberta, Canada

<https://www.ualberta.ca/biochemistry/people/faculty/holger-wille.html>

<https://www.ualberta.ca/prion-centre/faculty-and-staff/holger-wille.html>

The infectious prion protein is characterized by a distinct, three-dimensional conformation, which results in the surface exposure of disease-specific epitopes. We have used insights into the structure of the infectious prion protein to create a structure-based prion vaccine that specifically mimics the surface of the infectious conformer. Efficacy trials in a genetic prion disease mouse model demonstrated a significant extension in the health-span of immunized mice versus unimmunized controls.

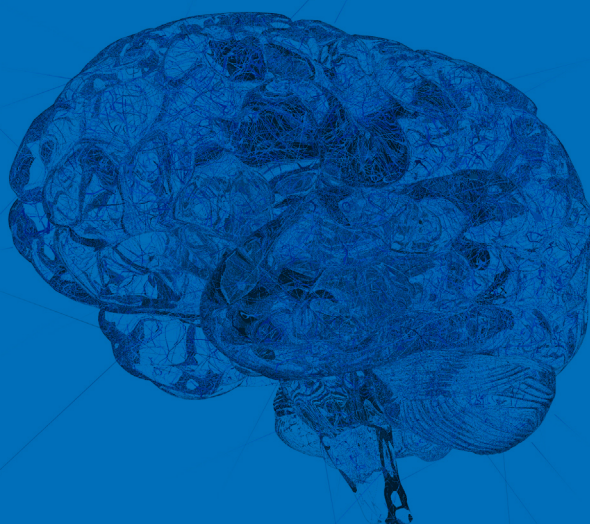


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